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Original Communications

STREPTOMYCIN AS AN ADJUNCT IN SURGICAL TREATMENT OF PULMONARY TUBERCULOSIS

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IT IS a pleasure to open this meeting with a discussion of the merits of streptomycin, the first and only specific therapeutic agent which has come to the assistance of the surgeon and phthisiologist since the institution of collapse therapy for pulmonary tuberculosis.

At the end of the twenty-five-year period ending in 1945, thoracoplasty, the major surgical collapse procedure, had probably reached the zenith of its possibilities as a therapeutic measure in terms of maximum percentage of cavity closure and sputum conversion with minimum mortality and morbidity. Contributing to this was a tremendous experience with the behavior of tuberculosis under surgical management, increased surgical skill, and progressive improvements in the ancillary factors of anesthesia, blood-loss replacement, improved pre- and postoperative care, smaller stage operations, etc. By far the greatest factor, however, in reducing mortality and morbidity in the operated group has been experience and skill in the selection of cases for operation, and the proper timing of operative interference. This has led to the general recognition of the so-called "good chronic" as the standard risk for thoracoplasty. It is in this group of patients that most clinics have been able to achieve a low operative mortality of 2 to 3 per cent, a low incidence of acute postoperative spread and exacerbation, and a rate of cavity closure and sputum conversion approximating 70 per cent. The factors which increase the operative risk, such as age, extent and activity of disease, bilateral involvement, toxic constitutional symptoms, extrapulmonary tuberculosis, cardiac impairment, large sputum output, marked reduction of the respiratory functional capacity, diabetes, etc., were also generally recognized. The combination of one or more of these factors relegated a large group of patients with cavitary disease to the status of substandard surgical risks. In

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many of these patients the preoperative bed rest waiting period was often prolonged, and a great many never did reach the status of a fair operative risk, and thus were denied the benefits of surgical collapse.

The mortality and morbidity statistics could be improved or worsened in accordance with the manner in which operative indications were limited to the standard risk group, or the boldness with which they were extended into the substandard risk group.

After 1942 following the stimulating work of Churchill and Klopstock, and its further extension by Overholt and Maier, resection surgery for tuberculosis began to take a place in the surgical armamentarium. The work of these early pioneers in the field was plagued not so much by operative mortality per se, as by a high incidence of fresh postoperative spread or exacerbation of old quiescent lesions attributed to dissemination of tubercle laden bronchial secretions during operation. This factor was improved to some extent by the Overholt face-down position during operation, but early and late exacerbation and spread continued to hinder the wider application of resection surgery to the problems of cavitary tuberculosis.

Such was the status of the surgical treatment of pulmonary tuberculosis, when in 1945 and 1946 the work of Hinshaw and others in the treatment of tuberculosis with streptomycin began to appear.

To summarize briefly: After one year to eighteen months clinical trial, the following were some of the facts about streptomycin that became apparent.

1. At long last there was a therapeutic agent tolerated by human beings which had a specific antibacterial effect on the tubercle bacillus.

2. While streptomycin had no rapidly effective curative action on chronic productive or cavitary tuberculosis, soft pulmonary lesions of recent origin tended to improve promptly.

3. Dosages of 2 Gm. or more per day over a prolonged period produced toxic manifestations characterized by impaired function of the eighth cranial nerve in a large proportion of treated patients. These toxic manifestations were decreased or eliminated by reduction of the dosage to 1 Gm. per day, and an effective in vivo concentration of the drug could still be maintained with this dosage.

4. Tubercle bacilli became resistant to streptomycin in varying periods, generally from 90 to 120 days, thus placing a time limit on the beneficial effects of the drug.

5. Laryngeal and tracheobronchial tuberculosis were benefited by parenteral streptomyin treatment with resultant improvement in nutrition, decrease in toxicity, and general improvement in the patients' condition.

Scrutiny of these facts led to the conclusion that streptomycin with its acknowledged beneficial effect on progressive lesions of recent origin, and its limited period of effectiveness, might be more useful as an adjunct in the surgical treatment of pulmonary tuberculosis than in any other mode of use. We hoped that it might improve our results from resection surgery and widen our indications by being prophylactic for the early and late postoperative

dissemination and exacerbation of quiescent lesions. We anticipated that it might improve the risk status of some of those in the substandard risk group for thoracoplasty, and shorten the time of their preoperative cooling off period, thus broadening the field of major surgical collapse therapy without undue increase in the morbidity and mortality.

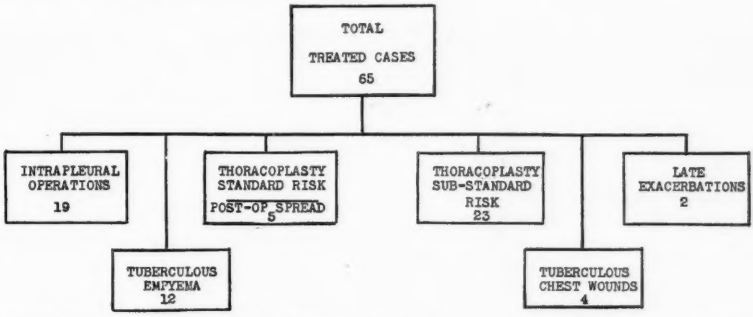


Fig. 1.—Streptomycin-treated cases, January, 1947, to January, 1948, Surgical Service, Triboro Hospital, New York, N. Y.

We had occasion during 1946 to observe the effects of the drug sporadically in a very few cases. Streptomycin in quantities sufficient for a fair clinical trial was furnished to us at Triboro Hospital as soon as possible within budgetary limitations by Dr. Edward M. Bernecker, Commissioner of Hospitals of New York, N. Y. This was in the early spring of 1947. All of the streptomycin used in this series of cases was provided free of charge to the patients by the Department of Hospitals, City of New York.

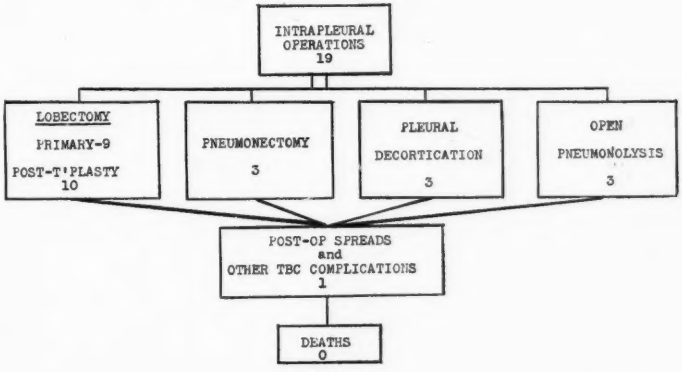


Fig. 2.

We are presenting a summary of our experience with the drug on the surgical service of Triboro Hospital during 1947, the first year of its use.

There was a total of 85 cases, 65 of the patients treated with streptomycin, and 20 thoracoplasties not treated with streptomycin. We have divided them into six groups as illustrated in Fig. 1. There were 19 intrapleural procedures including the resection cases; 23 substandard risk thoracoplasty cases; 5

cases of postoperative spread or exacerbation in a series of 25 standard risk thoracoplasty cases with no preoperative streptomycin treatment; 12 cases of tuberculous empyema; 4 tuberculous chest wounds, and 2 late exacerbations following surgery done in previous years.

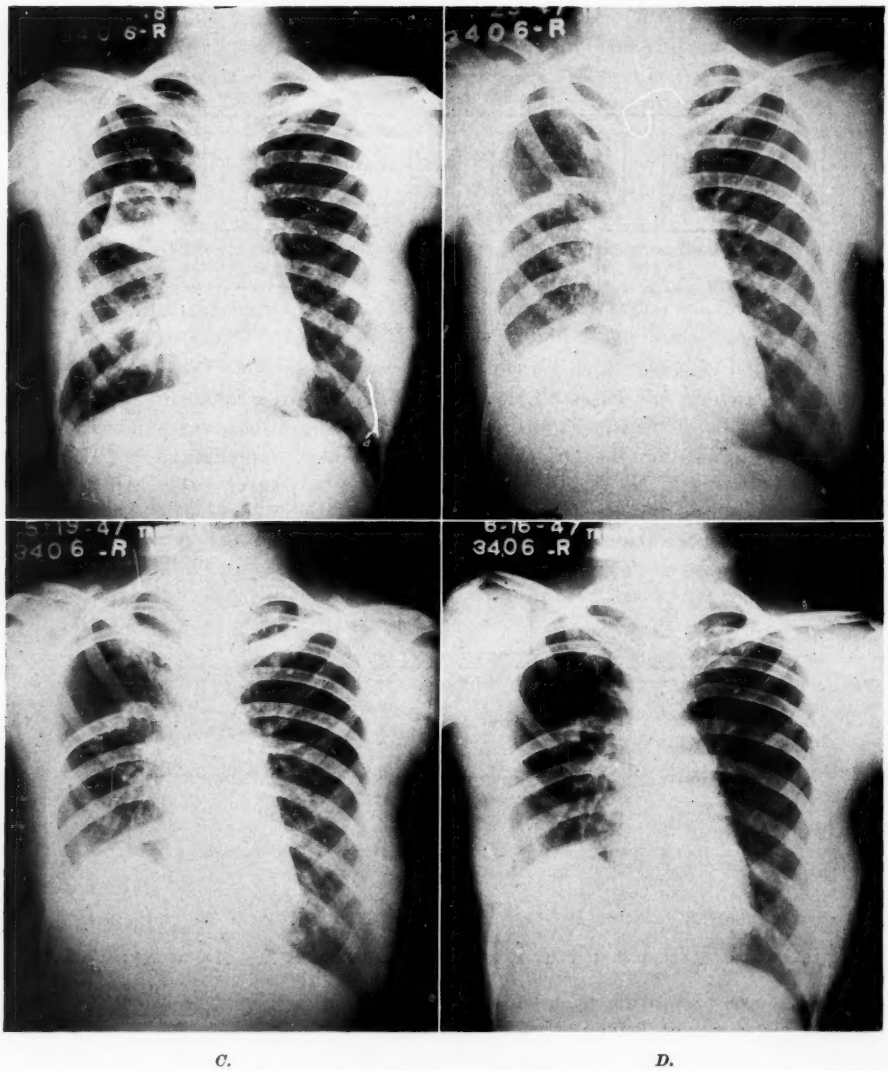
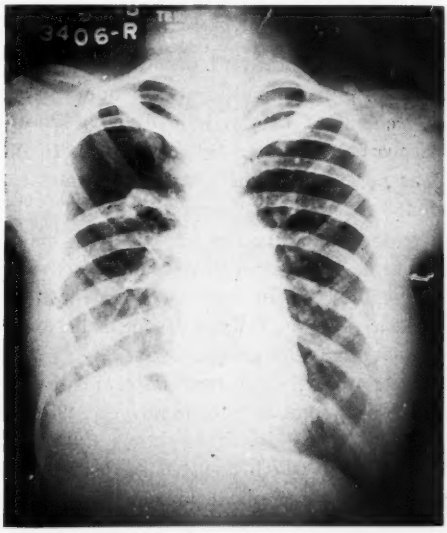


Fig. 3, *A* to *D* (Case 1).—*A*, Dec. 17, 1946, preoperative. *B*, April 23, 1947, one month postoperative, lobectomy right upper lobe and right middle lobe. *C*, May 19, 1947, two months postoperative. Note exudative lesion in expanded residual lower lobe. *D*, June 16, 1947, lesion receding after one month of streptomycin therapy.

All patients soon after the institution of streptomycin therapy showed a marked subsidence of cough, diminution in the daily sputum output, and diminution in the bacillary content of the sputum. This was particularly dramatic in patients with copious outputs of 8 to 10 ounces of sputum per day, and was usually accompanied by rapid improvement in the patient's general condition, decrease in toxicity, improved feeling of well-being, and improvement in the nutrition. These changes often took place within ten days to two weeks after the initiation of therapy; in some cases the progress was slower. Most patients on preoperative streptomycin therapy came to operation practically dry as far as sputum output was concerned, and we feel that this is one of the most important contributions of the drug to the prevention of postoperative pulmonary complications.



E.

Fig. 3, *E.*—March 5, 1948, one year postoperative.

The operations in this series were performed by a number of different surgeons. The majority of the operative procedures were performed by the resident staff with the supervision and assistance of the attending staff.

We have grouped all the intrapleural procedures together (Fig. 2) comprising 10 lobectomies, 3 total pneumonectomies, 3 pleural decortications, and 3 intrapleural pneumonolyses done in bilateral cases.

Streptomycin was used as follows in the decortication and open pneumonolysis cases: 1 Gm. per day was given for seven days preoperatively and fourteen days postoperatively. The postoperative course in all 6 cases was benign, and there were no tuberculous or other serious complications.

In all the resection cases, streptomycin was given intramuscularly in dosages of 0.5 Gm. every twelve hours for three to four weeks preoperatively

and for ninety days postoperatively, with the exception of one patient who received streptomycin fourteen days preoperatively and fourteen days postoperatively.

CASE REPORTS

CASE 1.—A 26-year-old white woman was admitted to Triboro Hospital in May, 1946, with a productive and cavernous lesion in the right upper and middles lobes (Fig. 3, *A*). On March 22, 1947, after fourteen days of preliminary streptomycin therapy, a lobectomy of the right upper and middle lobes was done. The postoperative course was benign and uneventful and streptomycin was discontinued fourteen days postoperatively (Fig. 3, *B*). On May 15, 1947, a symptomless early infiltration in the apex of the right lower lobe was noted on checkup x-ray examination (Fig. 3, *C*). Streptomycin therapy was reinstituted and continued for 120 days. The infiltration disappeared in about four weeks (Fig. 3, *D*) and the patient's course since has been without complication. Fig. 3, *E* shows the status of the patient in March, 1948, one year after operation.

All the remaining cases in the resection group came to operation with marked reduction in sputum output, and practically dry in this respect. The postoperative courses were unusually benign and uneventful. No contralateral or ipsilateral spreads occurred in the immediate postoperative period, and no late spreads or exacerbations have been noted up to date. The Overholt face-down position was not used in these operations, and so is not a factor to account for low incidence of postoperative complications.

We have no untreated control series in which the patients were operated upon during the same time interval as this group of cases. However, the immediate postoperative results are in contrast with those of a small series of resections for tuberculosis done at Triboro Hospital between the years of 1942 to 1946. In this prestreptomycin group, 3 out of 21 lobectomies developed bronchopleura fistulas, empyema, and contralateral spread, of which the patients died from eight to nine months postoperatively. Two out of four patients with total pneumonectomies for destroyed lungs developed immediate postoperative contralateral spreads which resulted in death of the patients.

The next two groups of thoracoplasties should be considered together. The first group of 25 patients had multiple stage paravertebral thoracoplasties without preoperative or postoperative streptomycin. The second group of twenty-three patients had multiple stage thoracoplasties with preoperative and postoperative streptomycin.

The two groups are not exactly comparable, as they were not selected on a consecutive alternating basis. Since the streptomycin budget in a Municipal Hospital was not unlimited, its use in the individual case had to be restricted to certain rigid indications. Before streptomycin could be prescribed, each individual case was evaluated and passed upon by a committee of the chiefs of the medical and surgical services. Under these circumstances it was felt by the committee that in thoracoplasty cases the limited streptomycin available should be reserved for the substandard risk patients, and for those who, due to complications, might not have been able to undergo major surgery without streptomycin therapy.

The first group of 25 cases (Fig. 4) were considered standard thoracoplasty risks according to the usual methods of case selection. They underwent 73

stages of thoracoplasty. In 5 of these cases acute exudative spread occurred after first or second stages. Streptomycin therapy was instituted immediately on recognition of the complication and continued for 90 to 120 days in 4 cases. In the fifth case clearing was so rapid and complete that streptomycin was discontinued after twenty-eight days. In 4 of these cases it was found that the remaining stages could be completed after two to six weeks' delay instead of the usual wait of six or more months. The patients so treated have done well.

One death occurred in this group. A patient in his mid-forties died suddenly on the third day following an upper-stage thoracoplasty. Autopsy showed pulmonary embolism.

The roentgenograms in the following case are illustrative of a standard risk patient who had ipsilateral spread following an upper stage thoracoplasty.

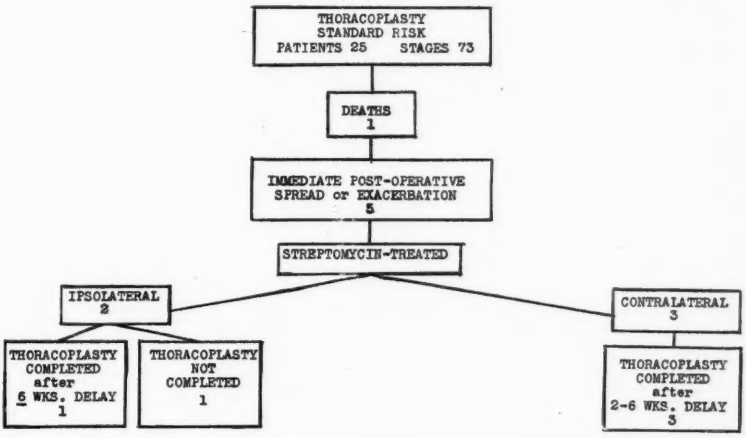


Fig. 4.

CASE 2.—A 46-year-old patient was admitted to Triboro Hospital for the first time in September, 1943, with bilateral upper lobe lesion and cavities in the left upper lobe. In spring, 1944, left pneumothorax was given for three months and abandoned because of ineffective collapse. July, 1944, the patient left the hospital against advice. In October, 1946, the patient was readmitted because of increased constitutional symptoms (Fig. 5, *A*). In mid-March, 1947, an upper-stage thoracoplasty was done without preoperative streptomycin. An acute exudative spread to the left lower lobe occurred immediately (Fig. 5, *B*). Streptomycin, 0.25 Gm. four times a day, was started and in five weeks sufficient x-ray resolution and remission of symptoms were noted, that it was deemed feasible to proceed with thoracoplasty (Fig. 5, *C*). The second stage was done on May 1 and the third stage on May 22, with uneventful postoperative course. Streptomycin was continued for 120 days. Sputum conversion with negative culture was obtained, and has been maintained to date (Fig. 5, *D*).

In the next group all 23 patients (Fig. 6) were considered substandard risks and were treated preoperatively and postoperatively with streptomycin. Eight had giant cavities or destroyed lungs with large daily sputum output. Five had contralateral pneumothorax or thoracoplasty. Three had previously active contralateral involvement, 2 had diabetes, and 5 others had large daily sputum output. After these patients were selected for possible thoracoplasty

they were placed on streptomycin, 0.25 Gm. intramuscularly four times daily, observed until constitutional symptoms and sputum output were considered reduced to a minimum, and advantage was taken of this optimum time to

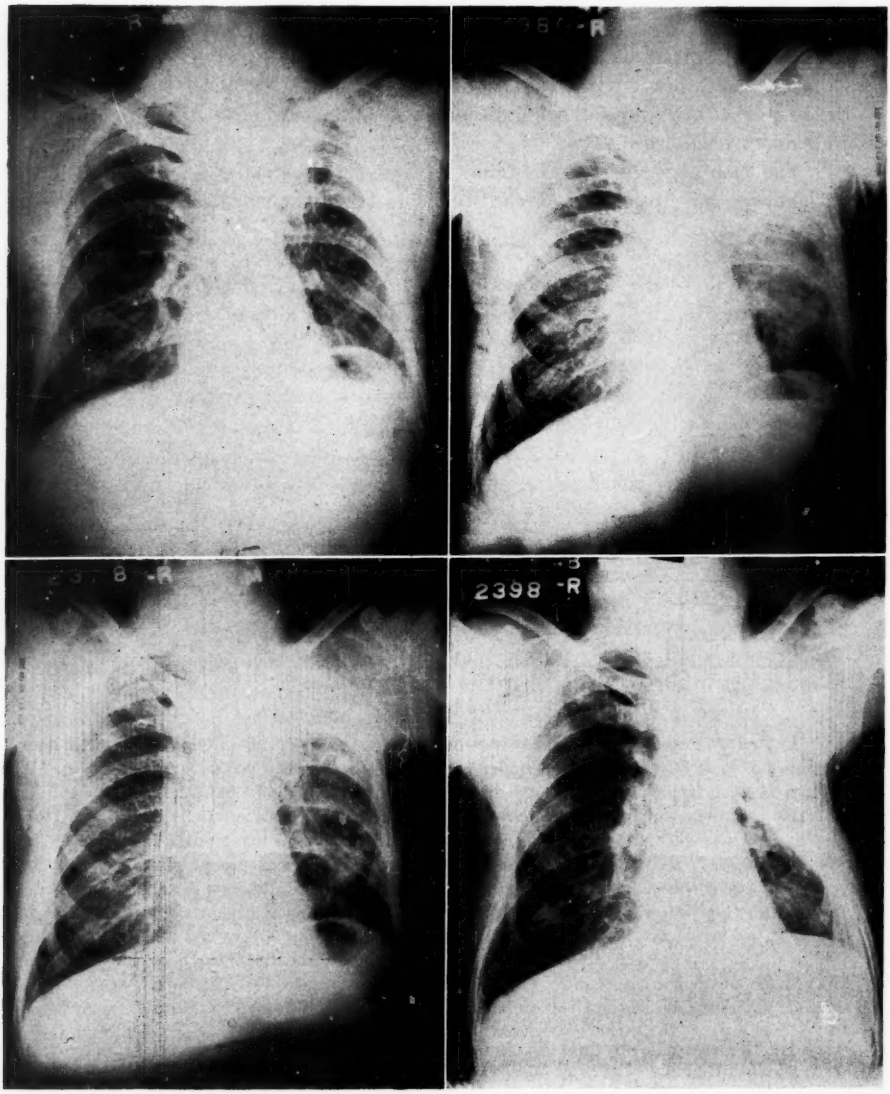


Fig. 5 (Case 2).—*A*, Immediately prior to left upper stage thoracoplasty. *B*, March 27, 1947, acute exudative spread in left lower lobe following upper-stage thoracoplasty. *C*, April 30, 1947, partial clearing of fresh exudative lesion in left lower lobe following one month streptomycin therapy. *D*, March 23, 1948, ten months after completion of thoracoplasty.

start the thoracoplasty. Thus the preoperative period of treatment varied. In the 8 cases with giant cavity or destroyed lung, the minimum preoperative treatment was twenty-eight days and the maximum forty-two days. In 2 of these cases concomitant laryngeal involvement cleared up completely during the preoperative treatment period. In all the cases of this sub-group of 8, streptomycin was continued postoperatively until 120 days of streptomycin therapy were completed. The contralateral pneumothorax and diabetic cases had a combined preoperative and postoperative total of 90 days' treatment. In the remaining cases the total treatment was 70 days each.

Fourteen of these patients had a pretreatment sputum output of 3 to 8 ounces per day. Nine had a sputum output of 1 to 3 ounces per day. In all cases there was a marked decrease in the sputum output, in some cases to 0 at the time the first stage was undertaken.

Twenty-two of these 23 patients underwent 71 stages of thoracoplasty with benign uncomplicated postoperative courses, and complete freedom from spread or exacerbation in all instances.

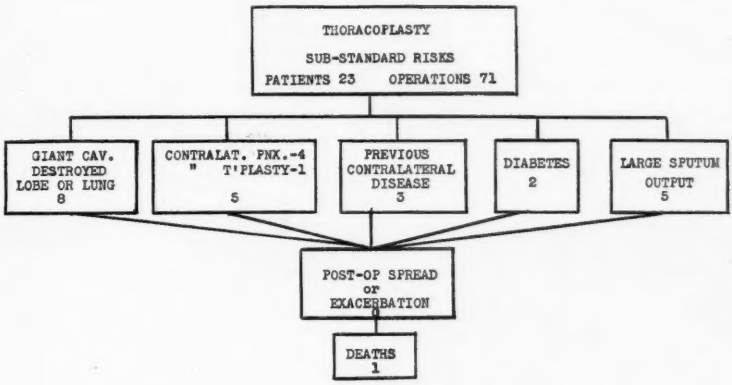
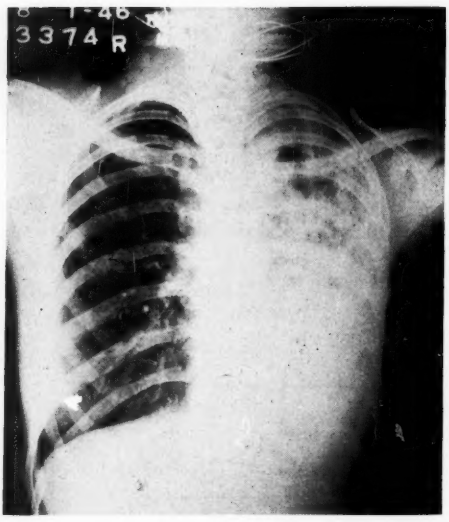


Fig. 6.

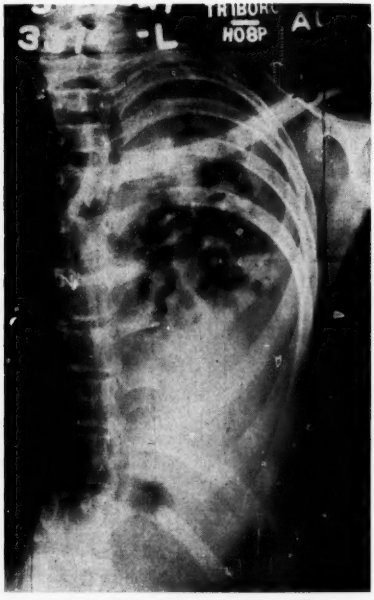
There was one postoperative death in this group. It was a sudden death on the ninth postoperative day following a second stage thoracoplasty. The postoperative course had been benign and uncomplicated, and the patient was apparently doing well. Autopsy was not obtained, so the cause of death was undetermined.

The x-ray films in Case 3 illustrate a substandard risk due to destroyed lung with multiple cavities and bronchiectasis, and large sputum output.

CASE 3.—An 18-year-old patient was admitted to Triboro Hospital in April, 1946, with an eleven-year history of pulmonary tuberculosis (Fig. 7, *A*). After one year of bed rest there was persistently elevated temperature, a daily sputum output of 8 to 9 ounces, heavily positive for tuberculosis, and mild laryngeal involvement with hoarseness. In April, 1947, decision was made to start collapse after preliminary streptomycin therapy. Pneumonectomy was contemplated, if thoracoplasty did not achieve arrest. The patient was placed on streptomycin, 0.25 Gm. four times a day, and response was dramatic. Within fourteen days the sputum output was reduced to less than 1 ounce per day, hoarseness and fever disappeared, and the patient began to gain weight. After twenty-eight days of streptomycin,

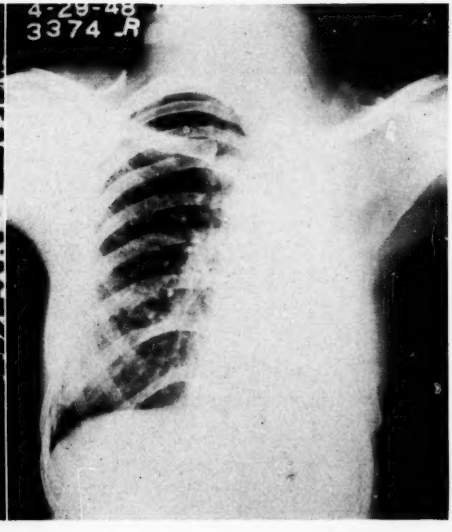


A.



B.

C.



D.

Fig. 7 (Case 3).—*A*, Aug. 1, 1946, preoperative. Multiple cavitation, destroyed lung. *B*, May 25, 1947, postoperative. First lower-stage thoracoplasty. *C*, July 28, 1947, postero-anterior tomograph about five weeks after final left upper stage. *D*, April 29, 1948, ten months post-thoracoplasty.

the lower first stage of a multiple stage thoracoplasty done from below upward was started (Fig. 7, *B*) and nine ribs were removed in four stages during May and June. Fig. 7, *C* is a roentgen tomographic view taken about four to five weeks after the last stage. Sputum conversion occurred soon after completion of surgery, and sputum has remained negative on culture up to the present time. Streptomycin was continued until a total of 120 days' treatment had been given. Fig. 7, *D* shows present status ten months postoperatively.

The next group (Fig. 8) comprises 12 cases of tuberculous empyema, 4 without demonstrable bronchopleural fistula, and 8 with bronchopleural fistulas.

The x-ray films in Case 4 illustrate treatment of a case of tuberculous-mixed empyema without bronchopleural fistula.

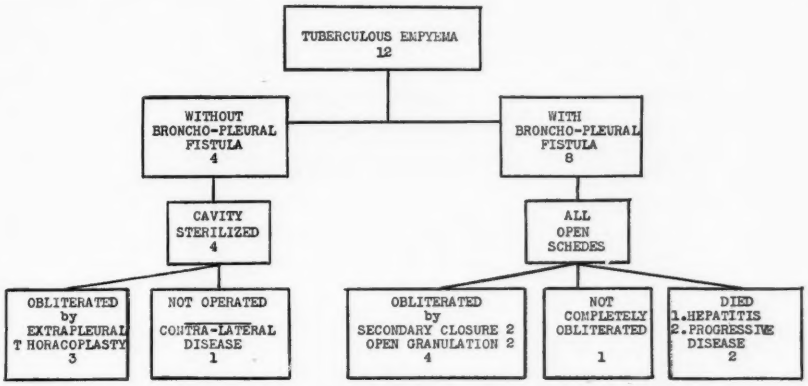


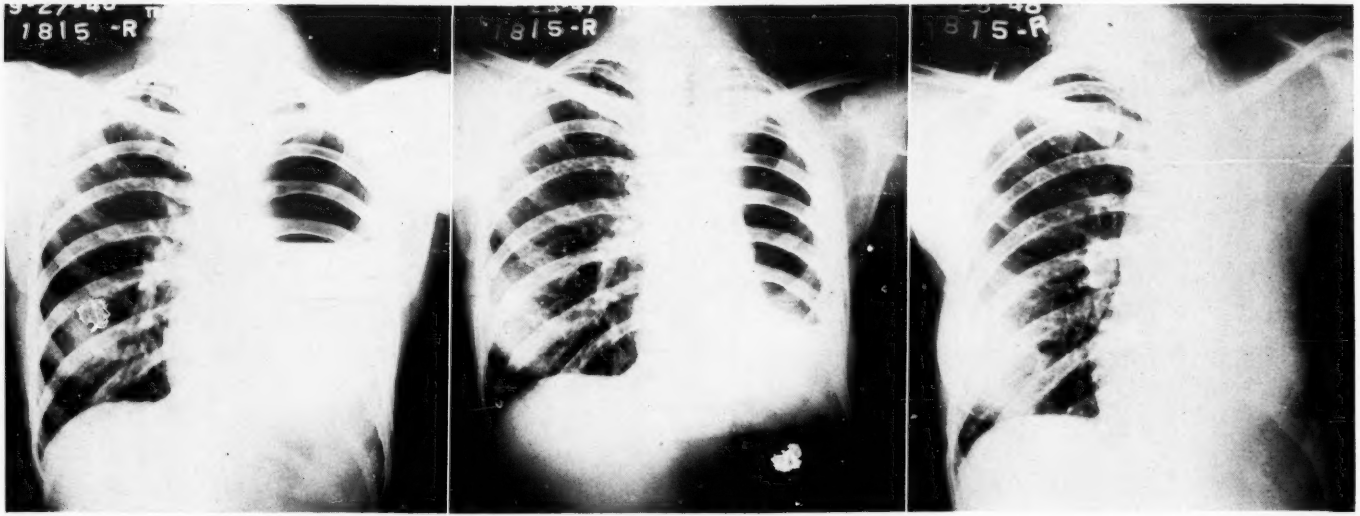
Fig. 8.

CASE 4.—A young white woman was readmitted to Triboro Hospital in September, 1946, with tuberculous-mixed infection empyema and pleurocutaneous fistulas (Fig. 9, *A*). Smear and culture showed tubercle bacilli and nonhemolytic streptococci. History dated back to 1939, with cavity in the left upper lobe treated by pneumothorax continuously. There was complete collapse of the left lung with bronchostenosis and persistently negative sputum. No bronchopleural fistula could be demonstrated.

After admission, twice-weekly thoracentesis with intrapleural instillation of 50,000 units of penicillin in 100 c.c. of saline rendered the pus free of streptococci but not of tubercle bacilli.

In the latter part of May, 1947, intrapleural streptomycin was started. Twice weekly the pus was evacuated by thoracentesis, and 1 Gm. of streptomycin diluted in 100 c.c. of saline was instilled. In a very short time the previously thick pus became thin and serous. After six weeks' treatment, fluid did not reform, and cultures for tubercle bacilli were sterile. The pleurocutaneous fistulae closed and in three months' time the patient gained thirty pounds in weight (Fig. 9, *B*). Subsequently a multiple stage thoracoplasty was done, and the left pleural space obliterated without resort to Schede operation (Fig. 9, *C*).

The three remaining patients in this group were treated with thoracentesis three times weekly. After evacuation of all fluid possible, 0.5 Gm. streptomycin diluted in 100 c.c. of saline was introduced into the empyema space. One patient had this treatment for ninety days before sterility was achieved; another for only twenty-two days. These three patients did not receive parenteral streptomycin. Streptomycin levels in the pleural fluid at forty-eight



A. *B.* *C.*

Fig. 9 (Case 4).—*A*, Sept. 27, 1946, tuberculous-pyogenic empyema, left. *B*, Sept. 24, 1947, after sterilization of empyema cavity with intrapleural penicillin and streptomycin. Prethoracoplasty. *C*, April 28, 1948, five months post-thoracoplasty.

to seventy-two hours after introduction of the drug varied from 10 to 160 millimicrograms per cubic centimeter. Simultaneous blood levels ranged from 5 to 10 μg irrespective of the pleural fluid concentration.

The empyema spaces in these three cases were rendered sterile and then obliterated by extrapleural thoracoplasty without drainage.

In the fourth case simultaneous parenteral streptomycin was given for ninety days because of extensive contralateral disease. The empyema space was sterilized, but the contralateral disease did not improve sufficiently to warrant thoracoplasty for obliteration.

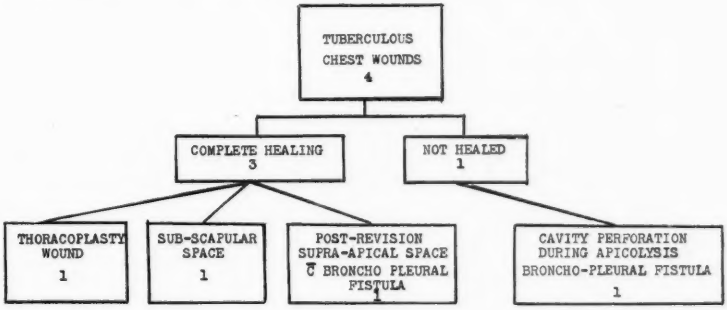

TUBERCULOUS CHEST WOUNDS 4
COMPLETE HEALING 3
NOT HEALED 1
THORACOPLASTY WOUND 1
SUB-SCAPULAR SPACE 1
POST-REVISION SUPRA-APICAL SPACE & BRONCHO PLEURAL FISTULA 1
CAVITY PERFORATION DURING APICOLYSIS BRONCHO-PLEURAL FISTULA 1

Fig. 10.

The 7 cases of tuberculous-mixed empyema with bronchopleural fistulas were all old cases that had residual empyema spaces after multiple stage Schede thoracoplasties. The treatment was to unroof surgically the residual space and leave it widely open. In two cases the thick infected fibrous plaque over the visceral pleura was decorticated without further mobilizing of the lung. These surgically exposed spaces were treated with streptomycin applied locally. One gram of crystalline streptomycin was thoroughly mixed with 4 Gm. of dry plasma powder. The wounds were liberally dusted with this mixture daily. No parenteral streptomycin was given. Dramatic healing was achieved with relatively small amounts of the drug in a very short time. The average amount used was from 14 to 28 Gm. for the entire treatment. Healing occurred in from two to five weeks with clean, granulating, shrinking wounds, and no pus formation at any time. In 4 cases complete healing was achieved by this method; in one case healing was not complete. One patient died of hepatitis, and one of progression of disease during treatment.

Blood levels were not demonstrable in the patients treated by topical application.

The next group of four tuberculous infected chest wounds, tabulated in Fig. 10, were treated parenterally and topically with streptomycin. In two postoperative tuberculous infected wounds, successful secondary closure and complete healing were achieved. In a third case, a tuberculous infected chest wound was due to cavity perforation following revision of a thoracoplasty. The bronchopleural fistula closed and the wound healed to the surface by granulation. In the fourth case, resulting from cavity perforation occurring

during apicolysis as a preparation for plombage, a bronchopleural fistula and tuberculous infected supra-apical space are still present. Streptomycin treatment was started, but had to be abandoned immediately because of extreme toxic sensitivity.

DRUG TOXICITY

One patient showed extreme sensitivity to the drug, and its use had to be abandoned. Only one patient developed vertigo of a significant degree after receiving 28 Gm. Seven patients showed slight toxic symptoms, such as headache and nausea. In these cases treatment was immediately discontinued for seven to ten days and then resumed, first with 0.5 Gm. as a daily dose and later, if no toxic signs recurred, the dose was increased to 0.75 Gm. daily. In 5 such cases treatment could be continued without any further toxic symptoms.

SUMMARY

Our experience with streptomycin as an adjunct in the surgical treatment of pulmonary tuberculosis in the Triboro Hospital during the year 1947 is presented. The results in 65 cases of pulmonary, pleural and chest-wall tuberculosis treated with streptomycin are summarized, and case histories typical of each group are cited. Twenty additional thoracoplasty patients untreated with streptomycin are included as controls. The efficacy of preoperative and postoperative streptomycin treatment in the prevention of postoperative complications in pulmonary resection for tuberculosis and thoracoplasty is evident. Beneficial effects of topical application of the drug in combination with open operations for bronchopleural fistulas and residual tuberculous empyema spaces are outlined. Dosage and mode of administration of the drug, and toxic reactions, are reviewed.

CONCLUSIONS

In our experience on the surgical service of Triboro Hospital as illustrated by the series of 85 cases presented herewith, streptomycin has been a most valuable adjunct in the surgical treatment of pulmonary tuberculosis, and has proved efficacious for the following indications:

1. Preoperatively and postoperatively for all pulmonary resections and intrapleural surgery on tuberculosis patients.
2. Preoperatively and postoperatively for all thoracoplastics considered substandard risks, or with complications such as contralateral pneumothorax, diabetes, etc.
3. For acute exudative postoperative spread, where streptomycin has not been used prophylactically.
4. Intrapleurally for pure tuberculous empyema without bronchopleural fistula.
5. In combination with open Schede thoracoplasty for tuberculous-mixed empyema with bronchopleural fistula.
6. In the infected chest wounds and sinuses.

(See discussion on page 55.)

THE ROLE OF STREPTOMYCIN IN THE SURGERY OF PULMONARY TUBERCULOSIS

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IN THE past year, 800 patients have been treated with streptomycin at Herman Keifer and The Maybury Sanatorium. About 300 more have been treated at our other sanatoriums. It was our intention to give, at this time, a detailed statistical report of our results in this series, but this proved to be wishful thinking, and impossible of accomplishment. We can, however, give a general summary of our observations to date.

We shall confine this preliminary report to the patients at the Maybury Sanatorium who have received streptomycin for pulmonary tuberculosis only (either with or without collapse therapy or other measures), and to those at Herman Keifer Hospital in whom major surgical procedures have been contemplated or have been completed.

Patients given the drug were in the follow groups:

Group 1. Those in whom we hoped that collapse or other surgical measures could be avoided or reduced in amount.

Group 2. Those in whom surgical procedures (contraindicated because of the patient's condition, extent of disease, etc.) could be made possible through streptomycin.

Group 3. Patients who received the drug as a prophylactic measure against spreads following surgical and collapse procedures, or to clear these spreads if they occurred, and to make the operation possible earlier.

Group 4. Patients with proved or suspected tracheobronchial disease.

We have had streptomycin available in sufficient quantities for extensive trial only since the autumn of 1947, and most of it since January, 1948. It is obvious, therefore, that it is too early for definite, reliable statistical analysis. Many patients have not yet finished the course of treatment, and others have had it too recently to report end results. We have, however, been forced to some very definite conclusions regarding the merits of the drug because the whole course of the surgical management of pulmonary tuberculosis has, in our clinic, been revolutionized since its use was begun.

In Group 1, composed chiefly of patients with early, minimal and moderately advanced disease, we have found that streptomycin has decreased the

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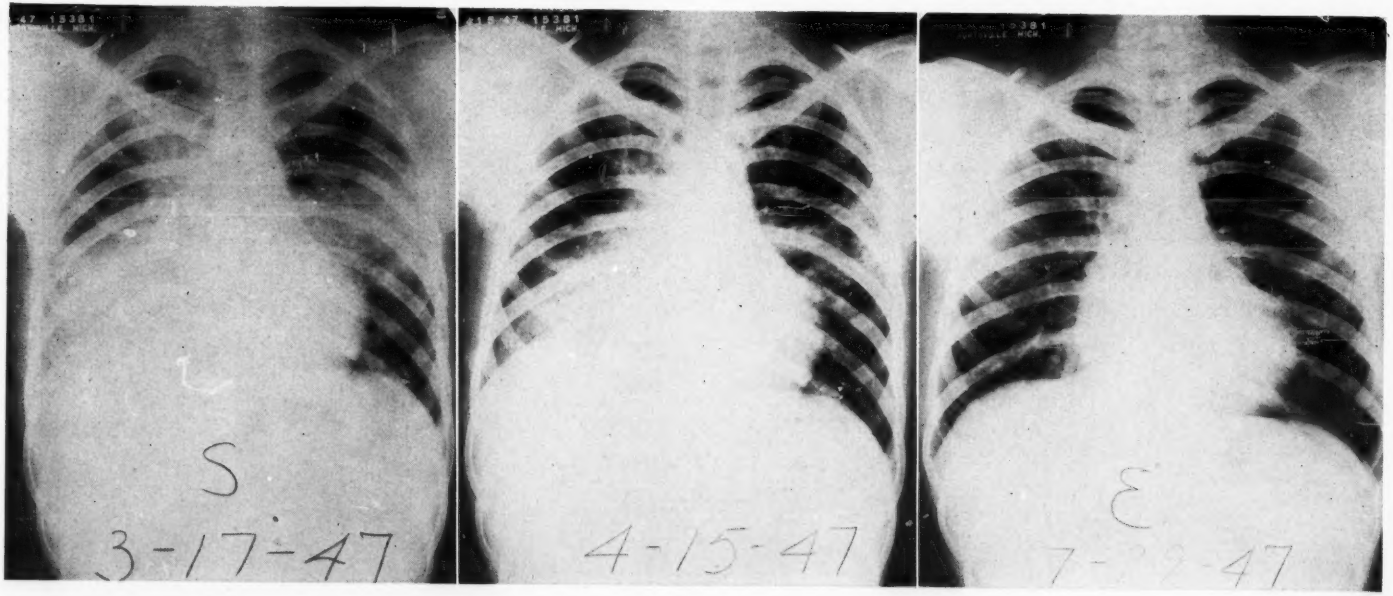
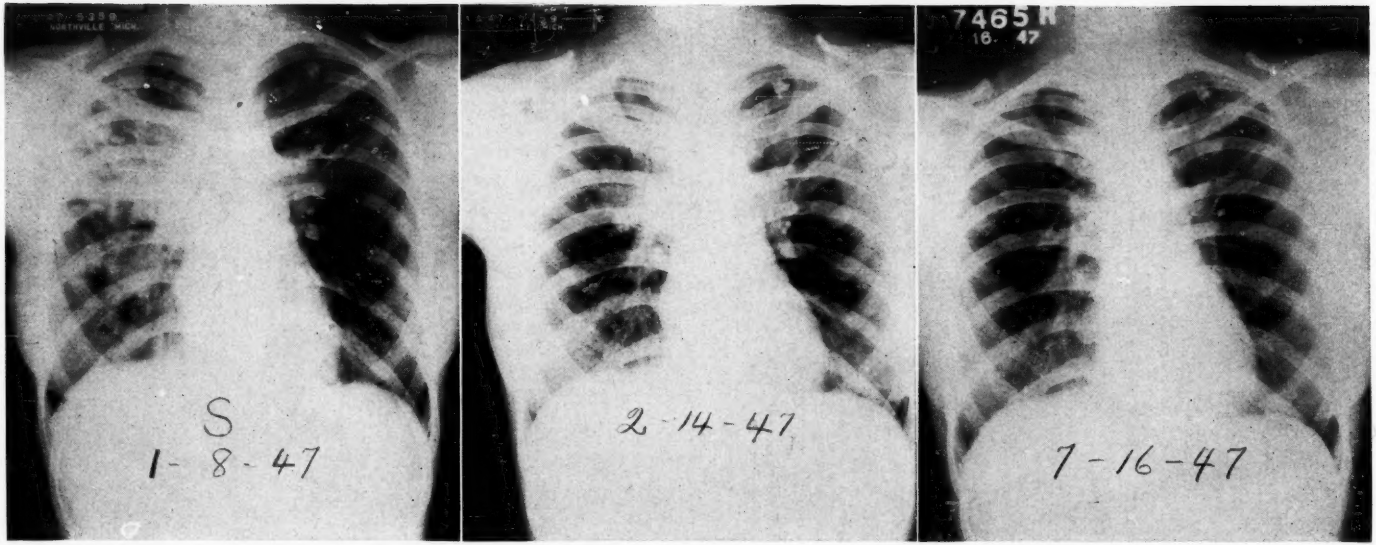
necessity of collapse measures by over 50 per cent (Fig. 1). Even in more extensive disease, the results are sometimes so startling that further procedures are found unnecessary to complete the arrest of the disease (Fig. 2). In the group of patients who have apparently been spared collapse measures, there are, of course, some who may need them later, while others who apparently need the assistance of some procedures to complete cavity closure and convert sputum may become entirely well without them for it is a routine observation that lesions continue to improve for months following the discontinuation of the drug. This seems more apparent in patients who are not receiving collapse measures. This group presents a difficult problem. If we wait too long before applying collapse procedures, the disease may reactivate, and spread. If we apply them early, there is the possibility that they may not have been necessary. We have tried to take the middle-of-the-road attitude, but we are sure we have added procedures which may not have been needed, and have also withheld them too long with unfortunate results. We do not know how much streptomycin a patient needs. It cannot be determined, after an arbitrary course of treatment, that its continuance might not be essential. Reactivations have occurred following treatment which, we are sure, would not have taken place if more streptomycin had been given. We have, in a number of instances, started the drug again in patients following these episodes, and have obtained excellent results (Fig. 3). This fact must be kept in mind in patients of any group. To prolong the treatment we should know the sensitivity of the organism, and of course this takes time, and if the sputum is negative it is impossible. If no complications exist we have, in this situation, frequently disregarded sensitivity and have obtained good results. In some instances, we found the patient just as sensitive after the course of treatment as he was before. The fear of patients becoming resistant to the drug is always with us, and while we believe with Hinshaw[1] and Feldman[2] that too much stress is laid on this danger, it cannot as yet be ignored. It is for this reason that the drug has been held in reserve by us when it seems possible that the disease may be arrested safely with collapse measures alone. Were this not the case, it is safe to say that the percentage of patients who have been spared collapse measures would be markedly increased. It is possible that, in the future, all patients will be treated with the drug when first seen, and without fear of resistance. Promin, amino salicylic acid, etc., along with streptomycin help some, but it is probable that more refinements will be forthcoming. It seems inconceivable, however, that any drug will ever be able to permeate dense, fibrotic scar tissue surrounding tubercle bacilli. It becomes our duty, therefore, to see that patients are treated properly before this stage is reached. It has been our observation, from roentgenograms, that lesions treated with streptomycin tend to heal by resolution or soft scar; from limited observation, our pathologist, Dr. Wm. Brosius, confirms this theory. Therefore, if patients are treated effectively early enough in the course of their disease, the problem of dense, fibrotic scar tissue should not present itself.



A. *B.* *C.*

Fig. 1.—Extensive bilateral disease in a very ill patient with positive sputum, temperature 104° F. *A*, Appearance before treatment; *B*, one month after treatment with streptomycin; *C*, four months after start of treatment.



A. *B.* *C.*

Fig. 2.—Extensive disease with multiple cavitation and positive sputum in a very ill patient. *A*. Appearance of chest before treatment; *B*, appearance one month after treatment with streptomycin; *C*, appearance six months after start of treatment.

In spite of our stated middle-of-the-road attitude, in this group we have tended, in patients with extensive, soft disease with cavitation and for whom thoracoplasty or resection was deemed advisable before streptomycin, to perform these operations in spite of marked clearing. Whether this is the proper

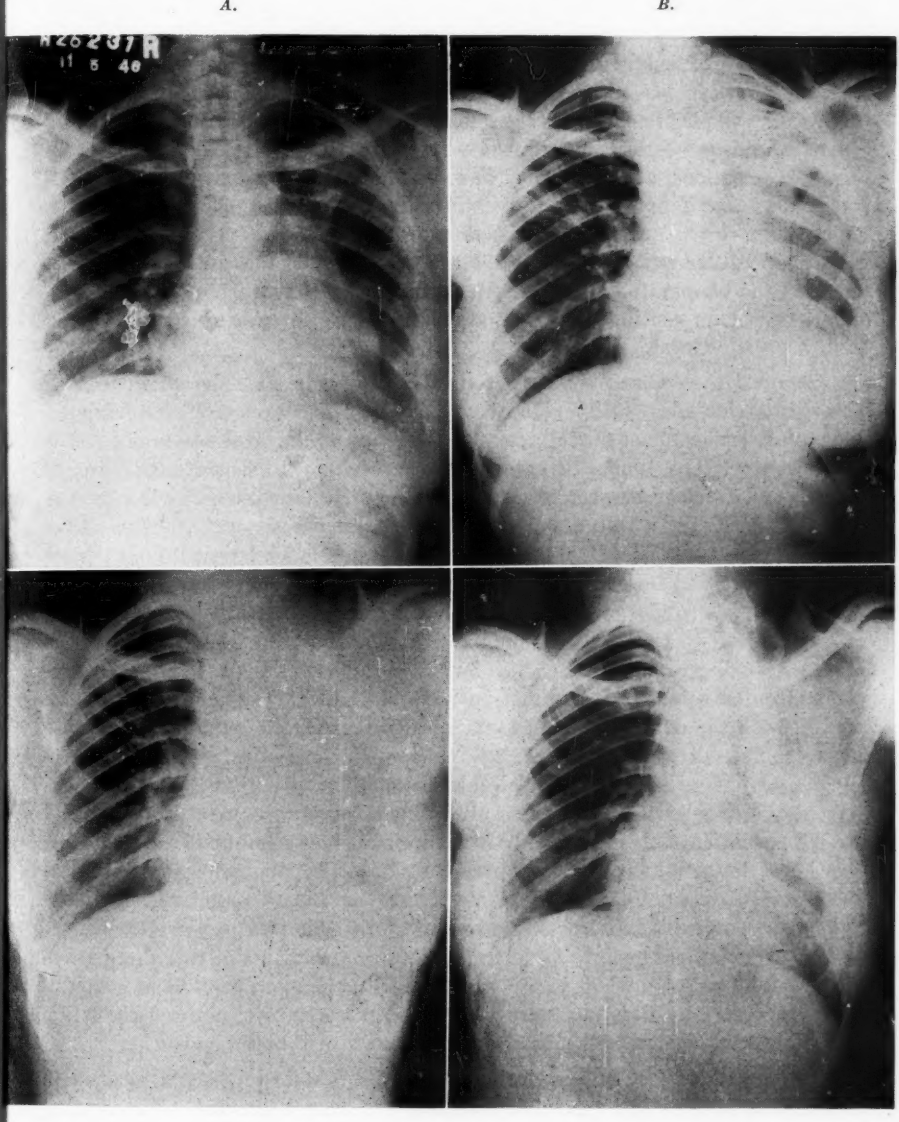


Fig. 3.—Intestinal tuberculosis in a very ill patient, seven months pregnant; temperature 103° F. *A*, Appearance of chest upon admission; *B*, appearance of chest after spread; *C*, right lung cleared under streptomycin; *D*, appearance following thoracoplasty.

course to follow can be determined only after much more time has elapsed and our experience broadened. In fact, what the future holds for all patients who have had streptomycin must await further observation.

In Group 2, we have found that the number of patients in whom surgical procedures (especially thoracoplasty) were possible was doubled by the administration of streptomycin. Many lesions, seen before administration of the drug, were so extensive and of such character that collapse measures could not be performed. Also, the condition of many patients was too grave, and there were complications such as gastrointestinal, peritoneal, pelvic tuberculosis contraindicating surgical procedures. Streptomycin is markedly effectual in these complications, and after they have subsided and sufficient clearing of the lesion has taken place, surgical procedures may frequently be completed with expectancy of good results. We have often seen patients extremely ill, with high temperature and dyspnea (some almost moribund and in oxygen tents), in whom the temperature became normal rapidly, the oxygen tent was removed, and the patients continued to improve making surgical procedures, with good results, possible later.

Group 3 somewhat overlaps Group 2, but will be considered separately. This group includes patients in whom major procedures are contemplated where soft lesions exist on the operation side, or an unstable lesion is present in the contralateral lung. Streptomycin is used here to prevent contralateral spread, and to clear or protect the contralateral lesions during and after the surgery. In Negroes and others with known lack of resistance, the use of the drug here is imperative. We are now operating on much softer lesions earlier and have observed fewer spreads since we began its use. We now believe that in all patients undergoing major surgical procedures it should be used prophylactically. Group 3 also includes those patients in whom a spread has occurred during or immediately following these operations regardless of previous streptomycin. It is our experience that these spreads clear much more readily with the drug, and with a marked decrease in the number of collapse measures necessary to assist them in doing so. The administration of streptomycin previously has not changed this observation. We have repeatedly restarted the drug with the same result as in those patients who have not had it. These patients obviously had not had a sufficient amount of the drug before operation. When so-called spreads occur, it is important, for statistical purposes, to distinguish between new, fresh lesions and reactivation of old lesions (or autotuberculinization) which are noted for their rapid clearing. A review of old roentgenograms is usually necessary to make this distinction. There can be no doubt that, in this group of patients, many months of hospitalization are saved. It is most probable that, in the future, marked reduction in the financial burden to the family or community will be achieved.

In Group 4, there is no question about the results in proved ulceration. These often heal as if by magic soon after the drug is started. The number of bronchoscopies performed for these lesions has been strikingly reduced. Prolonged treatment with silver nitrate application is no longer necessary.

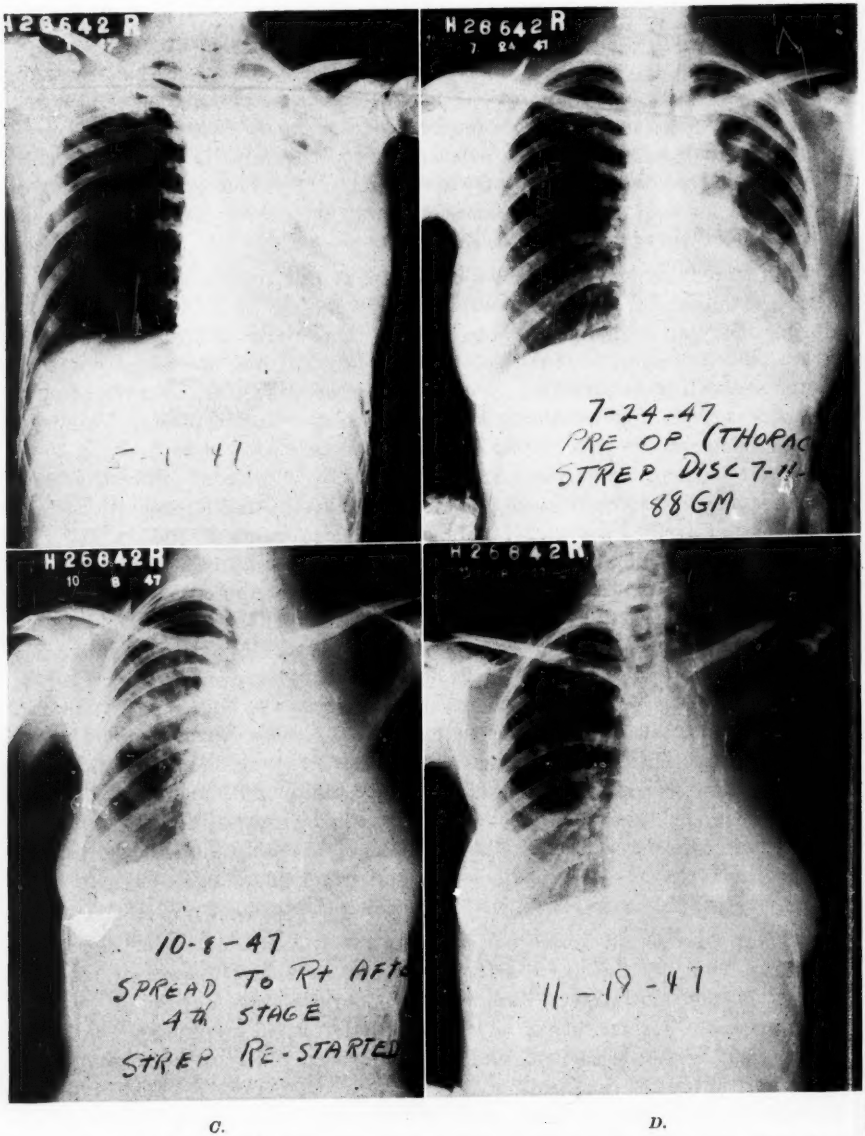
Bronchoscopy is now done for diagnosis, and again after streptomycin therapy, the latter being virtually unnecessary, however, except for statistical purposes because it is so rare not to find ulcers healed after streptomycin therapy. It is our observation, however, that there is often much endobronchial ulceration, beyond the vision of the bronchoscope, which is the cause of atelectasis, blocked cavities, and positive sputum. If patients suspected of having such lesions are given streptomycin, with early and marked clearing of the atelectasis and reduction in the size of the cavities, we can be sure that the diagnosis was correct, and that the bronchi have again become patent. However, if the results are negligible, we can presume that the condition is either healed stenosis or parenchymal disease. Because sometimes it is difficult to differentiate between atelectasis and parenchymal disease by roentgenogram, we feel that some of the excellent results sometimes reported for old fibrotic lesions were probably in reality atelectasis (Fig. 4).

As stated earlier, we find it impossible, at this time, to break down this series in detail and evaluate results with any degree of accuracy. However, during the year beginning in March, 1947, there were 89 first stage thoracoplasties performed without the use of streptomycin. Only sporadically was the drug used until autumn of that year. During the same year, however, streptomycin was given to 101 patients to prepare them for thoracoplasty. Following its administration in this group, 20 were found no longer in need of it. These 20 were classified, before treatment, as follows: favorable, 10; unfavorable, 5; hopeless, 5. There are 50 patients now ready and waiting for operation. This group was classified before streptomycin as: favorable, 9; unfavorable, 16; hopeless, 25. We have found that there are fewer spreads following thoracoplasty, and also fewer residual cavities. This is explained by the marked effectiveness of streptomycin in blocked cavities which are often displaced but unchanged in size; after one or two stages of thoracoplasty, these frequently close after streptomycin. The drug should be used, however, before rebridged bone occurs to prevent approximation of cavity walls and healing. In this regard, it must be kept in mind that the size of a cavity revealed by roentgenogram does not at all represent the amount of destruction of lung parenchyma. Cavities (especially blocked ones) have a tendency to balloon, and give a distorted idea of the amount of pathology present. Frequently, it is impossible to determine whether blocked or partially blocked cavities exist. Therefore, it seems obvious that streptomycin should be used as a prophylactic measure in all patients undergoing thoracoplasty.

There were twenty-three patients who received streptomycin prior to resection. Nine of these had extensive tracheobronchial disease or unstable lesions in the contralateral lung which made resection impossible prior to streptomycin. It was given to the remainder as a prophylactic measure. There was one late empyema, and one death occurred from hemorrhage, but no other untoward incidents occurred from operation in this group. In twenty patients, streptomycin was used during the course of decortication because of pleural involvement, etc., and no complications arose in this group.

following operation except one bronchopleural fistula. Their postoperative course, however, was smoother, and pleural reactions were less marked, and cleared more promptly.

A. B.



C. D.

Fig. 4.—*A*, Film before streptomycin; *B*, reveals marked clearing two months after streptomycin—atelectasis gone, cavity remaining; *C*, film showing spread following thoracoplasty in spite of previous streptomycin; *D*, clearing after restarting streptomycin.

At the Maybury Sanatorium, thirty-three patients who were thought to need collapse measures before streptomycin did not need them afterward. Twenty-six others who were thought to need major procedures needed only minor ones after streptomycin therapy. Sixty-three, in whom collapse or surgery was impossible before use of the drug, were able to have these procedures. In sixty-seven, there was no change in the pre- and post-treatment recommendations. In this group, there was considerable improvement in the lesions and symptoms, in most patients, and they were made better candidates for the procedures recommended. Fourteen were given the drug for fresh spreads. All of these cleared without the addition of other collapse measures. In thirty-three, no collapse was possible before or after treatment. This group can be classified as failures. In the remainder of the patients, it is too early for conclusions.

We have attempted not to give tiresome and confusing figures of statistics, but to show, in general, what in our experience streptomycin can be expected to accomplish in the surgical management of pulmonary tuberculosis, and to suggest a somewhat routine course for its application.

As would be expected, our results were most striking in soft mixed, and most recent lesions. However, occasionally, in apparently old, fibrotic lesions, excellent results have been obtained. In almost all patients, some clearing of the lesions and clinical improvement have been noted. One of our great problems is to know what to do with these "old chronics" in whom the outlook seems hopeless. If we give streptomycin to them as a last resort, we shall probably tend to put the drug into disrepute. Relatives, who are told that the patient's condition is hopeless, however, will always feel better if they know that everything possible has been tried. Even in terminal patients, it is probable that the temporary symptomatic improvement, the feeling of well-being, decreased cough, and lessened discomfort make administration of the drug worth while. At least, their last days are made easier. We feel that it is a doctor's function to get people well if possible, but if this cannot be done, he must at least make them as comfortable and as happy as lies within his power. Streptomycin does so many wonderful things when it is properly employed that we do not believe its prestige will be seriously damaged following this philosophy.

In our experience, the results of streptomycin therapy, in properly selected patients, have frequently been so amazing that there is an inclination to be overzealous in our attitude toward it. We believe, however, that our policy should be one of conservatism for fear that charlatans and quacks, and those unfamiliar with its use and complications, will employ it indiscriminately, and cause more heartache and suffering than can be offset by their results. Even at the present time, it is being used by some men as a substitute for bed rest and the proper collapse measures. These men employ it in ambulatory patients, with positive sputum, who are living at home with their families or others, thus spreading the disease to many innocent victims. Meanwhile, the patients are receiving inefficient and inexcusable treatment. It cannot be emphasized

too often that streptomycin is not a substitute for but is an adjunct to bed rest and proper collapse measures.

One will not find perfect accord regarding the efficacy of the drug even among the best men in the profession. Those who are unfortunate enough to work in hospitals or sanatoriums where most patients have lesions, of the old chronic, fibroid type will not be enthusiastic about the use of streptomycin, but it must be remembered that all "old chronics" have become so, in most instances, because proper treatment was not instituted earlier. They were all, at one time, patients with soft, early lesions readily amenable to treatment.

One cannot conclude a discussion of streptomycin without dwelling on the complications which sometimes follow its use. In the early days, excessive amounts of the drug were given, and there were many serious and permanent complications. Eighth nerve involvement, vestibular involvement, kidney damage, skin eruptions, etc., were common. Great fear was expressed that the drug would fall into disrepute. At the present time, although we are not sure exactly how much of the drug is necessary to control disease in a given patient, we do know that much smaller doses, given once a day, will accomplish the desired result, in most instances, with far less danger of complications. At the Maybury Sanatorium, we are giving 1 Gm. once each day for six weeks. At the Herman Keifer Hospital, we give ½ Gm. once each day for twelve weeks. We are not certain which is the better method. Possibly much smaller dosage will suffice in many instances. With our present dosage, we have noticed a marked decrease in complications. Permanent significant damage virtually does not exist, and while frequently there are encountered vestibular disfunction and skin eruptions, these usually subside with the withdrawal of the drug. It can usually be started again later without repetition of these manifestations. Where expected results were not obtained during routine treatment, we have occasionally increased the dosage or prolonged its use.

This program has sometimes given results not obtained with the previous regime. There is a lot we do not know about streptomycin, but our knowledge is ever increasing. We are sure that streptomycin is the greatest single contribution we have had to date to aid us in our efforts to eradicate tuberculosis.

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1. Hinshaw, C. H.: Personal communication.
2. Feldman, W. H.: Personal communication.

(See discussion on page 55.)

EXPERIMENTAL AND CLINICAL STUDIES OF THE ROLE OF STREPTOMYCIN IN THE PLEURAL CAVITY

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WASHINGTON, D. C.

STREPTOMYCIN was first described by Waksman[1] in 1944. In 1945 Feldman[2] demonstrated that streptomycin exerted a protective effect in experimental tuberculosis in the guinea pig. Hinshaw[3] later reported beneficial effects on human tuberculosis treated with streptomycin.

Various investigators have studied the absorption of streptomycin injected intravenously and intramuscularly. For example, Adcock[4] has shown that 100,000 units (0.1 Gm.) of streptomycin given intravenously immediately produced a streptomycin blood level of 16 micrograms per cubic centimeter; this level fell quickly. At the end of one hour the streptomycin blood level was 5 micrograms per cubic centimeter or less. Zintel[5] gave 600,000 units (0.6 Gm.) of streptomycin intravenously and immediately produced a blood level of approximately 33 micrograms per cubic centimeter. After two hours there was a blood level of nearly 20 micrograms per cubic entimeter. At the end of six hours the blood level had fallen to zero.

One hundred thousand units (0.1 Gm.) of streptomycin given intramuscularly produced a maximum streptomycin blood level of approximately 7 micrograms per cubic centimeter one hour after injection. The blood level fell gradually over a ten-hour period to 1 microgram per cubic centimeter. Zintel employed 600,000 units (0.6 Gm.) of streptomycin intramuscularly, which caused a gradual rise to a maximum blood level of about 20 micrograms per cubic centimeter in three hours. This level fell gradually to 10 micrograms per cubic centimeter at the end of six hours.

Experimental observations by Stebbins,[6] on dogs, indicated that 100,000 units (0.1 Gm.) of streptomycin given intravenously produced an immediate blood level of 20 to 30 micrograms per cubic centimeter. Four hours later the blood level had fallen to 2 to 3 micrograms per cubic centimeter.

Since the beneficial effects of streptomycin on human tuberculosis have been demonstrated, it is reasonable to assume that the local use of streptomycin in the human pleura for tuberculous effusions or tuberculous empyema might be desirable.[7] Moreover, the local use of the antibiotic, after pulmonary resections for tuberculosis, could be expected to reduce the incidence of tuberculous empyema. This investigation was undertaken to determine whether or not streptomycin injected into the pleural cavity might produce deleterious effects on the pleura serosa and to determine the absorption rate of streptomycin from the pleural cavity.

Read at the Twenty-eighth Annual Meeting of The American Association for Thoracic Surgery, Quebec, Canada, May 31, June 1, 2, 1948.

From the Department of Surgery, George Washington University Medical School, Washington, D. C.

Research Grant from Medical Research and Development Board, S.G.O., U. S. Army.

METHODS

Dog Experiments.—Nine apparently healthy mongrel dogs weighing about 8 kilograms were used. There were no apparent wound infections nor any deaths.

Intravenous nembutal plus intratracheal ether anesthesia was used. With aseptic precautions the left or right pleural cavity was entered by resecting a piece of rib 3 to 4 cm. in length. One hundred cubic centimeters of isotonic saline were then placed in the pleural cavities of three dogs. One hundred cubic centimeters of isotonic saline containing 0.5 Gm. of streptomycin were placed in the pleural cavities of six dogs. The streptomycin was calcium chloride complex* and had been freshly dissolved. The pleura, muscles, and skin were closed with fine, interrupted silk sutures. Pleural fluid and blood samples were collected from the animals for streptomycin titer assay.

On the seventh postoperative day the wounds of all nine dogs were reopened. Biopsies of the pleura were taken from the pleura involved in the scar and from the pleura away from the scar. The gross appearance of the pleural cavities of the two series of dogs seemed the same. There were small adhesions of the lung to the pleura in a few of the dogs, but there were no adhesions in most of the dogs. The wounds were reclosed and the biopsies of the pleura were fixed in 10 per cent formalin for microscopic section and examination.

Human Experiments.—In twelve human patients 0.5 Gm. of streptomycin in 10 c.c. of saline was instilled in the pleural cavity at the close of a thoracotomy. The pleural cavities in these cases had been opened by resecting a rib, and various types of thoracic operations had been carried out. Some of the pleural cavities were drained by an intercostal catheter which was unclamped at various intervals after the instillation of the streptomycin. In all cases 100,000 units of penicillin in 10 c.c. of isotonic saline were installed along with the streptomycin. At various intervals postoperatively 5 c.c. of sterile clotted blood were withdrawn for streptomycin titer assay.

The sterile clotted blood samples were kept refrigerated until the assay was done. This varied from a few hours to a few days later. The method used was a broth dilution technique devised by Romansky.[8] Except as otherwise noted, whenever penicillin was present, penicillin antibiotic activity was destroyed by the addition of penicillinase to the broth culture tubes.

RESULTS OF THE DOG EXPERIMENTS

Absorption Studies.—The study on four dogs receiving 0.5 Gm. of streptomycin in the pleural cavities at open thoracotomy is summarized in Fig. 1. In three dogs, fluids taken from the chest immediately after the streptomycin had been instilled was found to contain 3,750 micrograms of streptomycin per cubic centimeter. Samples of pleural fluid were collected by thoracentesis from four dogs two hours after streptomycin had been instilled. These samples had, respectively, 100, 500, 375, and 1,650 micrograms of streptomycin per cubic centimeter. At the same time that this pleural sample was taken, venous blood was also taken for analysis. These levels were, respectively, 20, 20, 20, and 10 micrograms per cubic centimeter. Chest fluid taken from a dog twenty-four hours after injecting streptomycin contained no detectable streptomycin. Blood taken twenty-four hours after injection of streptomycin into the chest contained, respectively, 1 and 0 micrograms per cubic centimeter in two different dogs. A more complete absorption curve for streptomycin was obtained in another dog. Blood samples were collected one-half hour, four hours, eight hours, and twenty-four hours after placing 0.5 Gm. of streptomycin in the pleural cavity of the

*Manufactured by Merck & Co., Inc., Rahway, N. J.

dog. These levels were, respectively, 25, 20, 5, and 0 micrograms of streptomycin per cubic centimeter. These data are illustrated in Fig. 2. Another absorption curve was determined by collecting blood samples at one hour, 7 hour and 24 hour intervals in another dog. These levels were, respectively, 25, 2.5, and 0 micrograms of streptomycin per cubic centimeter. These data are illustrated in Fig. 3. In all the dogs studied the absorption of streptomycin from the pleura was rapid.

FIGURE NO. 1

STREPTOMYCIN LEVEL MICROGMS/C.C.

	INITIAL CHEST FLUID	CHEST FLUID 2 HOURS LATER	BLOOD 2 HOURS LATER	CHEST FLUID 24 HOURS LATER	BLOOD 24 HOURS LATER
DOG 2		100	20		1
DOG 3	3750	500	20		
DOG 4	3750	375	20	0	0
DOG 5	3750	1650	10		

Fig. 1.—Streptomycin absorption data from four dogs.

Pathologic Studies.—Microscopic sections were made of the biopsies of the pleura taken from the three saline control dogs and the six dogs receiving streptomycin. The pleurals taken away from the thoracotomy scar in the saline and in the streptomycin experiments are essentially the same. Giant cells and fibroblasts are seen in the pleural scars. It is apparent that these giant cells represent a foreign body response induced by the presence of silk sutures, since microscopic sections reveal no appreciable difference in pleuras which received saline or streptomycin.

RESULTS IN HUMAN EXPERIMENTS

There were twelve human cases studied. Six of these patients were considered to have unscarred pleuras, while in two cases the pleura was moderately scarred and in four the pleura was markedly scarred.

Unscarred Pleuras.—The first human study was conducted on a patient who had a resectable carcinoma of the esophagus and in whom the pleura seemed

normal. On the first postoperative day 0.5 Gm. of streptomycin was injected into the pleural cavity through the intercostal drainage catheter. The catheter was then clamped off to permit absorption of the streptomycin. Venous blood samples were collected 1, 2, 6, and 8 hours later. The levels were 5, 5, 2.5, and 2.5 micrograms per cubic centimeter. These results are illustrated in Fig. 4.

The second human case was a patient who had a portion of the chest wall resected because one rib contained a metastasis from a thyroid carcinoma. The pleura seemed uninvolved. Samples were taken at 30 minutes, one, two, four, six, and eight hour intervals. The catheter was unclamped just after the second

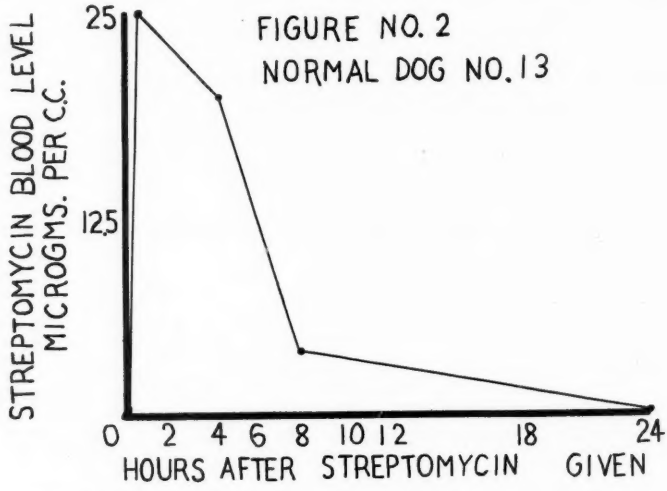
FIGURE NO. 2
NORMAL DOG NO. 13
STREPTOMYCIN BLOOD LEVEL MICROGMS. PER C.C.
25
12.5
0 2 4 6 8 10 12 18 24
HOURS AFTER STREPTOMYCIN GIVEN

Fig. 2.—Streptomycin absorption from the pleura of a normal dog.

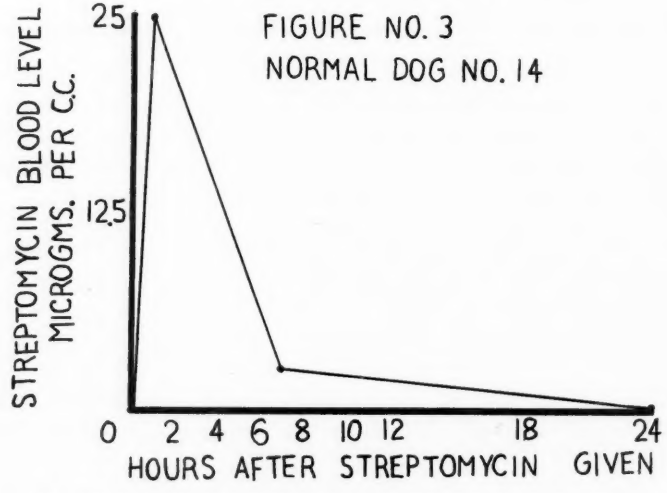
FIGURE NO. 3
NORMAL DOG NO. 14
STREPTOMYCIN BLOOD LEVEL MICROGMS. PER C.C.
25
12.5
0 2 4 6 8 10 12 18 24
HOURS AFTER STREPTOMYCIN GIVEN

Fig. 3.—Streptomycin absorption from the pleura of a normal dog.

hour sample was collected. The levels were 25, 20, 5, 5, 2.5, and 2.5 micrograms per cubic centimeter. These data are illustrated in Fig. 5.

The third human study was done on a patient who had an inoperable carcinoma of the lung where the pleura was uninvolved and where no intercostal catheter was used. No penicillinase was available. Levels were taken at thirty minutes, one, two, four, eight, and twelve hours. The levels were 50, 37.5, 20, 10, 5, and 2.5 micrograms per cubic centimeter. These data are illustrated in Fig. 6.

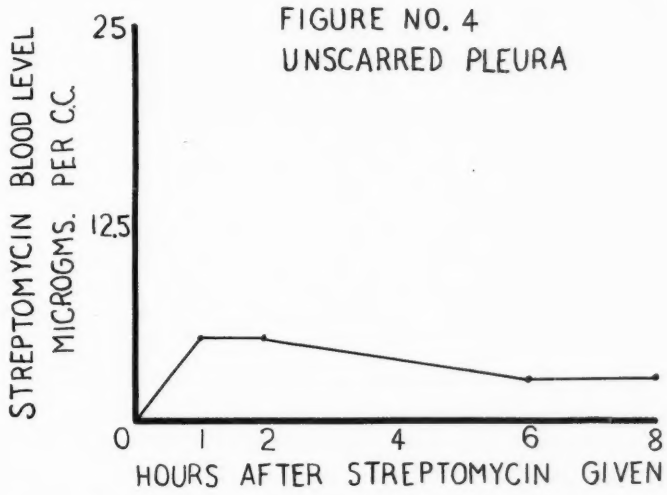

Fig. 4.—Streptomycin absorption curve from unscarred pleura, Case 1.

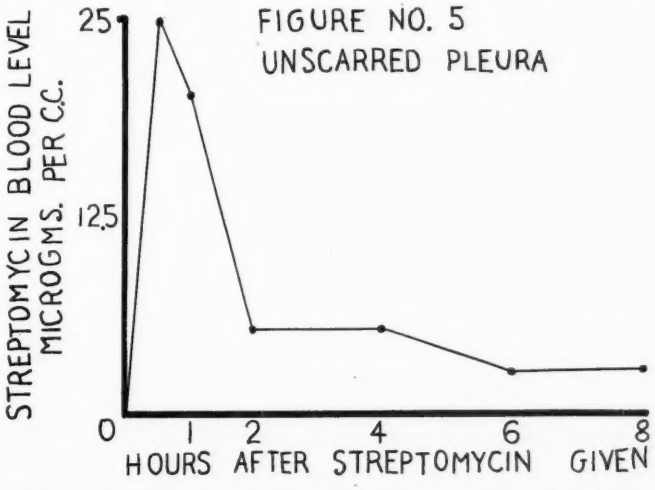

Fig. 5.—Streptomycin absorption curve from unscarred pleura, Case 2.

The fourth patient studied had an exploratory thoracotomy. Inflammatory nodes were found, and the pleura seemed normal. Blood levels were taken at thirty minutes, one, two, four, and six hour intervals. These levels were 12.5, 5, 5, 5, and 3.75 micrograms per cubic centimeter. These data are illustrated in Fig. 7.

The fifth patient studied had a mediastinal xanthoma removed. At the time of exploration the pleura seemed normal. Blood levels were determined

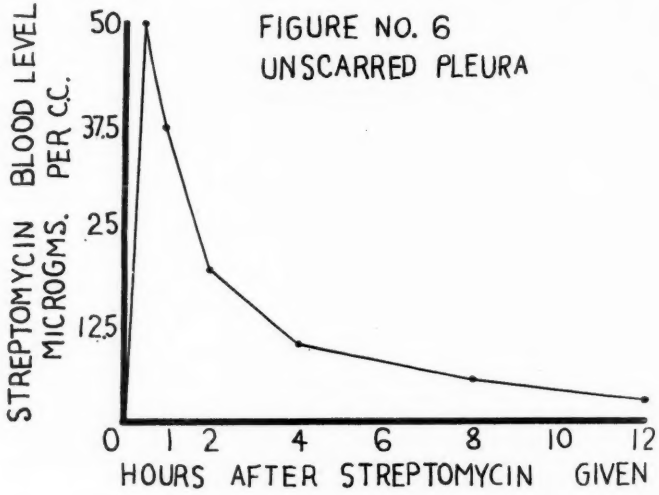

Fig. 6.—Streptomycin absorption curve from unscarred pleura, Case 3.

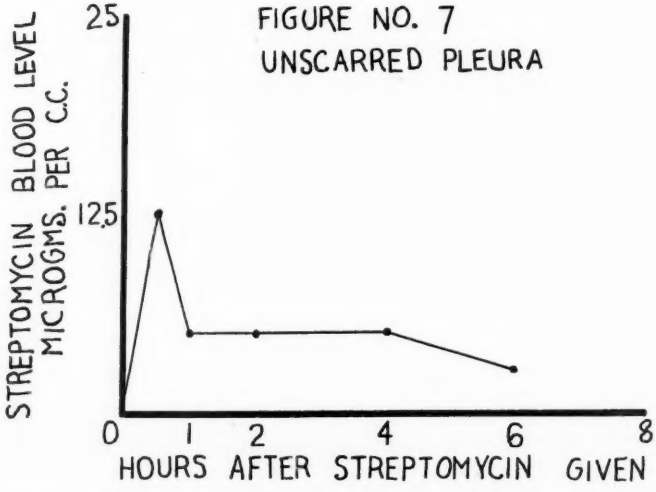

Fig. 7.—Streptomycin absorption curve from unscarred pleura, Case 4.

at thirty minutes, one, two, and four hour intervals. The levels were 25, 12.5, 10, and 5 micrograms per cubic centimeter. These data are illustrated in Fig. 8.

In the sixth case a thoracic exploration was performed. The pleura was found to be normal. Levels were taken at thirty minutes, one, two, four, and eight hours. The levels were respectively 25, 12.5, 10, 5, and 2.5 micrograms per cubic centimeter. These data are illustrated in Fig. 9.

Moderately Scarred Pleuras.—A moderately scarred pleura was found in a woman who had an open pneumonolysis performed for pulmonary tuberculosis.

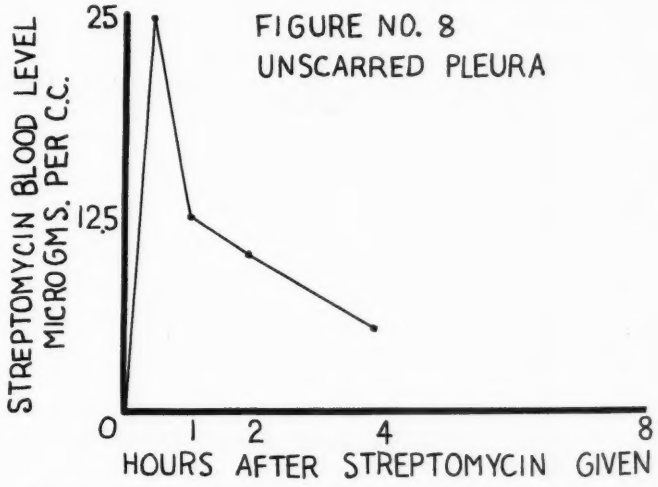

Fig. 8.—Streptomycin absorption curve from unscarred pleura, Case 5.

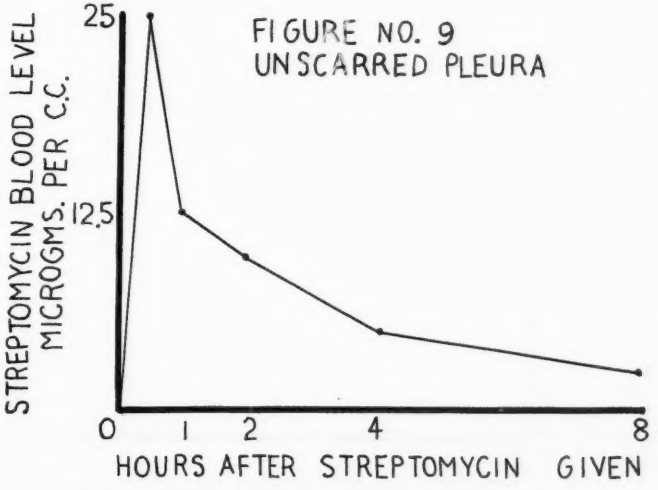

Fig. 9.—Streptomycin absorption curve from unscarred pleura, Case 6.

She had received 0.5 Gm. of streptomycin intramuscularly thirteen hours prior to operation. No intercostal catheter was used. No penicillinase was available. Blood samples were determined at thirty minutes, one, two, eight, and twelve hour intervals. The blood levels were found to be 22.5, 12.5, 12.5, 2.5, and 2.5 micrograms per cubic centimeters. These data are illustrated in Fig. 10.

The second patient who was considered to have a moderately scarred pleura had a left lower lobectomy and lingulectomy performed for bronchiectasis. There were a moderate number of adhesions present. An intercostal catheter was used. Blood samples were done at thirty minutes, one, two, four, and eight

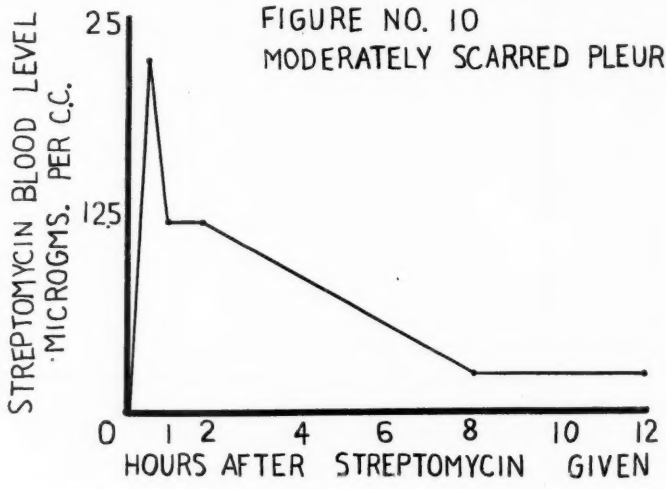

Fig. 10.—Streptomycin absorption curve from moderately scarred pleura, Case 7.

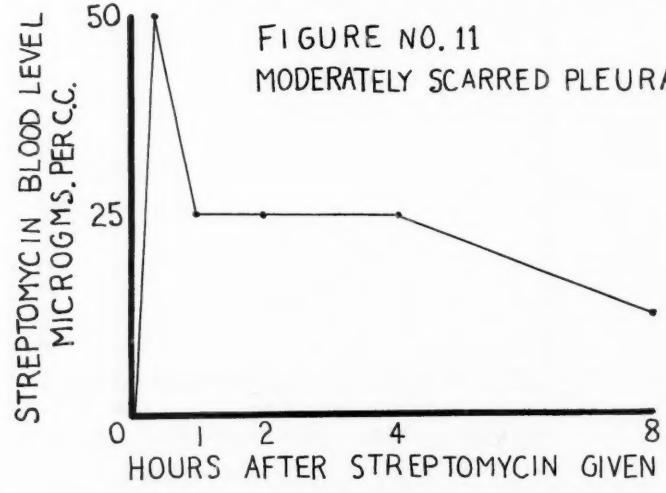

Fig. 11.—Streptomycin absorption curve from moderately scarred pleura, Case 8.

hours. The levels were found to be 50, 25, 25, 25, and 12.5 micrograms per cubic centimeter. These data are illustrated in Fig. 11.

Markedly Scarred Pleuras.—The first patient who was considered to have a markedly scarred pleura had a pneumonectomy performed for pulmonary tuberculosis. The patient had already had three stages of thoracoplasty performed and received streptomycin, 0.5 Gm., thirteen hours prior to surgery. There was no available penicillinase. Blood samples were withdrawn at thirty minutes, one, two, four, six, and eight hours. These samples were found to contain 12.5, 10, 5, 3.75, 2.5, and 1.25 micrograms of streptomycin per cubic centimeter. These data are illustrated in Fig. 12.

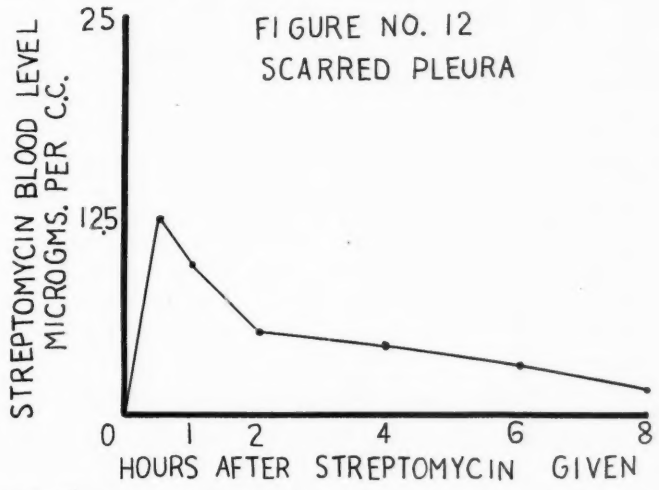

Fig. 12.—Streptomycin absorption curve from markedly scarred pleura, Case 9.

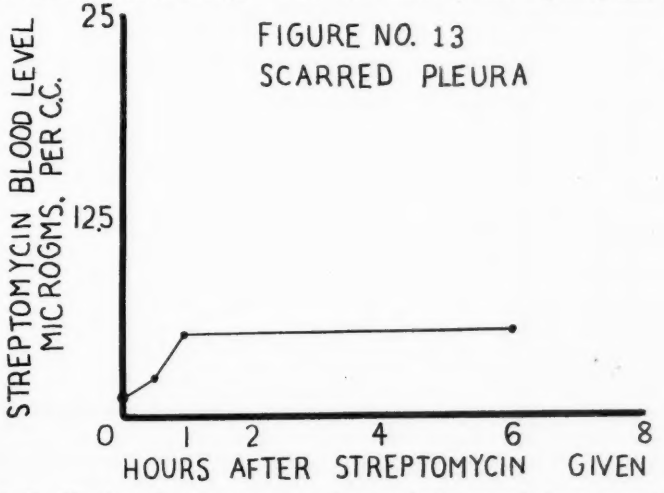

Fig. 13.—Streptomycin absorption curve from markedly scarred pleura, Case 10.

The second patient with markedly scarred pleura also had a pneumonectomy performed for pulmonary tuberculosis. She too received 0.5 Gm. of streptomycin about twelve hours before operation. Blood samples were withdrawn before injecting the streptomycin, and then 30 minutes, 1 hour and 6 hours later. The levels were 1.25, 2.5, 5, and 5 micrograms per cubic centimeter. These data are illustrated in Fig. 13.

The third patient having a markedly scarred pleura had a pneumonectomy for tuberculosis. Blood samples were withdrawn at thirty minutes, one, two, and four hour intervals. The blood levels in these samples were 25, 25, 10, and 5 micrograms per cubic centimeter. These data are illustrated in Fig. 14.

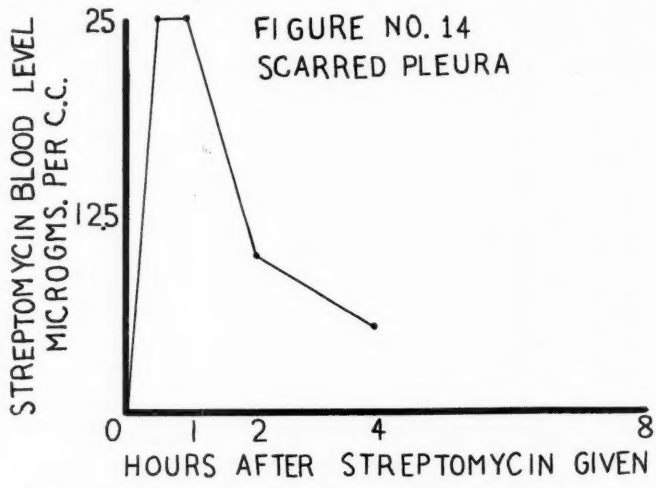

Fig. 14.—Streptomycin absorption curve from markedly scarred pleura, Case 11.

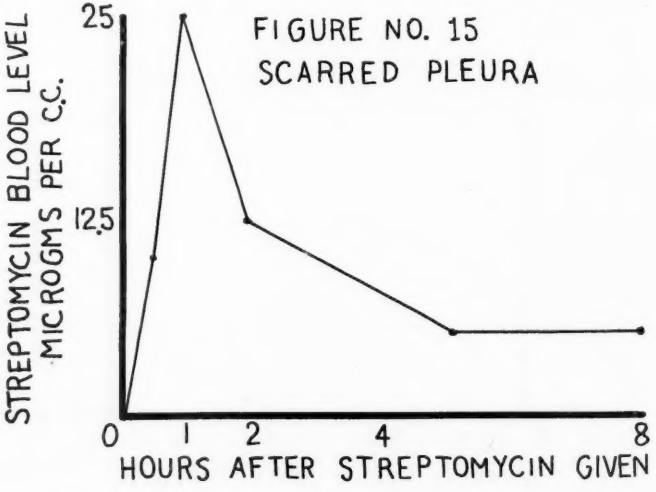

Fig. 15.—Streptomycin absorption curve from markedly scarred pleura, Case 12.

The fourth patient with a markedly scarred pleura had a pneumonectomy for carcinoma of the lung. The pleura was involved and was markedly scarred. Blood samples were withdrawn at thirty minutes, one, two, five, and eight hour intervals. These levels were found to be 10, 25, 12.5, 5, and 5 micrograms per cubic centimeter. These data are illustrated in Fig. 15.

SUMMARY

This paper describes experiments to determine the pathologic effect and the absorption rate of streptomycin from the the pleural cavity.

Operations were performed on nine dogs. Three of these dogs received 100 c.c. of saline into the pleural cavities, and then had a biopsy taken from the pleura seven days later. Six of the dogs received 0.5 Gm. of streptomycin in 100 c.c. of saline into the pleural cavities. Streptomycin assay studies were carried out on pleural fluid and venous blood. The pleura was biopsied seven days after injection.

The absorption rate of streptomycin from the pleuras of dogs was rapid and the maximum blood levels were reached in thirty to sixty minutes.

There were no apparent differences in the microscopic picture of the pleura from the animals receiving saline and the animals receiving streptomycin.

Twelve human patients received streptomycin intrapleuraly. These twelve cases can be subdivided into six cases of unscarred pleuras, two of moderately scarred pleuras, and four of markedly scarred pleuras. The absorption curves were similar in all three types. The absorption is rapid, being maximum usually in thirty minutes, and falls to low levels in six to eight hours.

CONCLUSIONS

No harmful effects were seen either in the gross or the microscopic picture of pleura removed from dogs seven days after the dogs received strepomycin in the pleural cavity.

The absorption of streptomycin from the pleura of dogs and human beings is rapid and high levels are reached.

Scarred pleuras seem to absorb streptomycin as well as unscarred pleuras.

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(See discussion on page 55.)

COMPARISON OF RESULTS IN TWO HUNDRED CONSECUTIVE RESECTIONS FOR PULMONARY TUBERCULOSIS

One Hundred Without Streptomycin Therapy and One Hundred With Streptomycin Therapy

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Philadelphia, Pa.

IN ATTEMPTING to draw a proper comparison between those patients with pulmonary tuberculosis who received streptomycin therapy before and after surgery with those who did not, it soon became apparent that there were many practical difficulties. For example, the cases in which streptomycin was not given were nearly all in an earlier group chronologically. Some extended back to 1941. Thus, many patients were operated upon without the advantage of more recent surgical and anesthetic improvements. This includes the face-down or Overholt position for surgery. Moreover, the first group was not subjected to routine postresection thoracic space reduction (usually thoracoplasty), nor did these patients have the benefit of our more critical present-day preoperative evaluation and greater experience in handling pre- and postoperative problems.

In contradistinction to this nonstreptomycin group, the routine use of streptomycin pre- and postoperatively was started in September, 1946. Thus, all of the streptomycin-treated series are less than two years postoperative. Perhaps some of them will develop complications or flare-ups in the future. On the other hand, some recent cases which are today sputum-positive may soon turn negative.

While the patients in the streptomycin-treated group have been operated upon on the senior author's thoracic surgical services by a more modern surgical and anesthetic technique, at least one-half were actually operated upon by younger and less experienced associates. Almost all of those in the prestreptomyicn group were operated upon by the senior author personally. The newer anesthesia methods and the face-down position have certainly been factors of great benefit in the more recent series but were also utilized in about one-half of the older series. Routine postresection reduction of the size of the thoracic cavity (usually thoracoplasty) was performed in nearly all of the patients in the more recent group, but also in at least three-quarters of those in the older group. It is true that we have had more experience in evaluating cases for surgery, and especially have benefited from the more recently developed pulmonary function tests. The most practical of the present physiologic study methods have been those of Ornstein, Herman, Friedman,

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and Friedlander.[1] We have, therefore, rejected a certain number of poor-risk cases in the second group. An opposing factor, however, is the fact emboldened by better results, have somewhat extended our indications and have at times "pushed our luck" in borderline cases. Also emboldened by the thought that we now had the "advantage" of streptomycin therapy, we have operated upon another type of poor-risk case. Thus, the latter series has included 14 cases of acute pneumonic tuberculosis, 6 cases with contralateral pneumothorax, and 14 cases with homolateral tuberculous empyema, among which 12 cases also had clinical bronchopleural fistulas. These latter were usually subjected to the formidable operation of extrapleural pulmonary resection plus excision of the empyema space.[2]

After consideration of all these difficulties, we nevertheless believe that some interesting and valuable conclusions may be drawn from comparison of the two groups. We were able to follow all of the early cases for at least one year, and the majority of them up to the present time. While there is a group of late untoward developments, most of our important surgical complications occurred early. The chief exception to this is the development of late tuberculous empyema in an unobliterated space remaining after pneumonectomy. Late tuberculous exacerbations which may develop in the same or opposite lung are frequently blamed upon the surgery but may well be due to the natural progress of the disease (which notoriously tends to bilateralization). Perhaps it may be due to an inadequate removal of tuberculous disease already existing at the time of resection. Ornstein[3] has stressed the necessity of bilateral planography in all tuberculous cases subjected to surgery; otherwise, either homolateral or contralateral cavities may be overlooked preoperatively.

Following is a breakdown of the indications for surgery in each group, with the treatment and operative mortality (Tables I and II).

TABLE I. INDICATIONS FOR RESECTION

INDICATIONS	CASES	WITH STREPTOMYCIN		SEGMENTAL	DEAD
		PNEUMONEC-TOMIES	LOBEC-TOMIES		
Severe bronchial stenosis	13	12	1	0	2
Associate or residual bronchiectasis	1	0	1	0	0
Ineffective temporary collapse	0	0	0	0	0
Ineffective permanent collapse	16	9	5	2	1
Very large cavity	6	4	2	0	0
Hilar cavity	2	0	2	0	1
Check valve cavity	3	1	1	1	1
Lower lobe cavity	3	0	3	0	1
Progressive cavitary disease (destroyed lungs)	22	20	2	0	2
Acute pneumonic disease	14	12	2	0	5
Tuberculoma	2	0	2	0	0
Bilateral localized	2	0	1	1	0
Elective	2	0	0	2	1
Bronchopleural fistula	12	9	3	0	2
Chronic mixed or simple empyema	2	2	0	0	0
Total	100	69	25	6	16
Surgical deaths	16	11	5	0	

TABLE II. INDICATIONS FOR RESECTION

INDICATIONS	CASES	NONSTREPTOMYCIN		SEGMENTAL	DEAD
		PNEUMONEC-TOMIES	LOBEC-TOMIES		
Severe bronchial stenosis	13	12	1	0	4
Associate or residual bronchiectasis	9	4	5	0	0
Ineffective temporary collapse	4	2	2	0	1
Ineffective permanent collapse	28	12	11	5	8
Very large cavity	15	5	7	1	1
Hilar cavity	0	0	0	0	0
Check valve cavity	3	0	2	1	1
Lower lobe cavity	4	1	3	0	1
Progressive cavitary disease (destroyed lungs)	12	10	2	0	9
Acute pneumonic phthisis	2	2	0	0	2
Tuberculoma	2	1	1	0	0
Bilateral localized	0	0	0	0	0
Elective	10	2	6	2	0
Bronchopleural fistula	0	0	0	0	0
Chronic mixed or simple empyema	0	0	0	0	0
Total	102	51	40	9	27
Surgical deaths	27	16	10	1	

DISCUSSION

The foregoing statistical breakdown tends to support certain impressions which have gradually developed. First, it is evident that resection for pulmonary tuberculosis is much safer in our hands since September, 1946 (Table III).

TABLE III. COMMON AND SPECIFIC POSTOPERATIVE COMPLICATIONS

	NONSTREPTOMYCIN		WITH STREPTOMYCIN	
	TOTAL	FATALITIES	TOTAL	FATALITIES
Spreads, contralateral	13	6	1	0
Spreads, homolateral	2	0	0	0
Empyema, pyogenic	4	0	0	0
Empyema, tuberculous	8	5	1	0
Empyema, mixed	1	1	2	0
Chest wall infection and sinus	7	1	2	0
Bronchopleural fistula (early)	7	3	2	2
Bronchopleural fistula (immediately after thoracoplasty)	4	0	1	0
Bronchopleural fistula (late)	3	1	1	0
Total	49	17	10	2

The most gratifying observation is that postoperative contralateral tuberculous spread is almost nonexistent on our service today. The one case of listed contralateral spread was that in which a bronchopleural fistula developed and in which the patient had been operated upon a few weeks previously for mixed infection tuberculous empyema due to acute cavity rupture following a closed pneumonolysis for tension cavity. It seems probable that the spread was related to aspiration of pleural contents and overwhelming infection.

Early postoperative tuberculous empyema did develop in three patients with pulmonary resection in the streptomycin group, one of whom had been

subjected to cavitary rupture and gross pleural contamination at operation. This is in contradistinction to thirteen cases of tuberculous empyema in the older group.

Development of bronchopleural fistula was also much less common in the streptomycin-treated group. Of the four cases of bronchopleural fistula in this group, two were in patients originally operated upon for bronchopleural fistula, and one was a case of acute pneumonic phthisis with contralateral disease under pneumothorax collapse. In an attempt to save much needed lung tissue, a multiple segmental resection was performed, although some questionably caseating lung tissue was left behind. This case was obviously a poor choice for any surgery. Another case was a pneumonectomy for destroyed lung. While there was no obvious reason for this man developing a bronchopleural fistula, it appeared a few weeks after thoracoplasty and was preceded by an unexplained fever throughout the surgical period. Perhaps he had a silent empyema of small size all that time.

Of the entire group of specific complications commonly seen after resection for pulmonary tuberculosis and which had occurred 49 times in the nonstreptomycin series, only 10 appeared in the group of streptomycin-treated cases. Whereas these complications caused 17 of the 27 deaths (63 per cent) in the first series, they caused only 2 of the 16 in the second series (15 per cent). Both of these deaths occurred in cases which would not have been considered operable at the time the first series was in progress. They were cases of mixed tuberculous empyema with bronchopleural fistula due to acute cavitary rupture.

The next noteworthy observation is the increased number of cases of extensive lung destruction (22) and acute pneumonic phthisis (14) in the streptomycin group, as compared to 12 of the former and 2 of the latter in the nonstreptomycin group (Table I). The surgical results were dramatically different in each series. Thus, of the 14 cases in both classifications in the nonstreptomycin group, 11 patients died (78.5 per cent). This is in line with the experiences of Sweet[4] and others with resection therapy for this type of case. On the other hand, of the 36 cases in the streptomycin-treated series only 7 patients died (19.4 per cent), 5 of these being in the acute pneumonic phthisis classification. Our overwhelming impression is that this marked reduction in mortality with these very serious cases is practically entirely due to the use of streptomycin. Reasoning along the lines of Pfuetze and associates[5] we would expect the suppressive effect of streptomycin in these cases of extensive to overwhelming pulmonary infection to produce a temporary reversion of the case to the status of less active and progressive disease. The surgical results should then become comparable to those in the more chronic classifications. Indeed, the mortality of the cases of "destroyed lung" under streptomycin therapy is quite satisfactory (9 per cent). The persistent high mortality (35.7 per cent) in the cases listed as acute pneumonic phthisis is probably due to the fact that the overwhelming infection cannot be as completely suppressed and that they still represent cases of fairly active tuber-

culosis at the time of surgery. We believe that the mortality would have been much higher in this group had streptomycin not been used. Packard[6] has urged a much longer preoperative period of streptomycin in such cases. However, we must not prolong this therapy to the point of losing the specific suppressive effect before surgery. Streptomycin-fastness of the concerned bacteria may well develop within six weeks.

Respiratory insufficiency, paradoxical breathing, and acute postoperative pulmonary edema were deemed causative of six deaths in the streptomycin-treated group, or 37.4 per cent of all deaths in this series. In the nonstreptomycin group only 2 deaths were listed as due to these causes, or 7.4 per cent of deaths in that series (Table IV and V). We believe that this increase in the later series is a direct reflection of our attempts to extend the indications somewhat in cases of borderline cardiopulmonary functional insufficiency. It can undoubtedly be reduced by a more careful screening of these cases *after* functional studies have been completed. Both Ornstein[3] and Crellin[7] have pointed this out in reviewing our series.

The remaining causes of death in both series are of wide variety and individual rarity. With the exception of a case of tuberculous pericarditis (operative opening of the pericardium) and one of tuberculous meningitis, they had no direct relation to the tuberculous process (unless we consider

TABLE IV. CAUSES OF DEATHS (STREPTOMYCIN GROUP)

Acute pulmonary edema	2
Bronchopleural fistula and mixed empyema	2
Contralateral spontaneous pneumothorax	1
Cardiac cessation on operating table	2
Paradoxical breathing	1
Hemorrhage, laceration of inferior vena cava	1
Respiratory insufficiency	3
Transfusion reaction (hemolysis)	1
Continuous oozing postoperatively	1
Amyloid disease with urema	1
Pulmonary embolism	1
Total	16

TABLE V. CAUSES OF DEATHS (NONSTREPTOMYCIN GROUP)

Postoperative cardiac failure (pulmonary edema)	1
Operative cardiac arrest	1
Tuberculous meningitis	1
Tuberculous pericarditis	1
Uremia due to amyloid disease	1
Acute postoperative anuria	1
3 days postoperative hemorrhage, tourniquet pneumonectomy	1
Chest wall and sinus infection	1
Inability to expectorate secretions postoperatively	1
Respiratory insufficiency	1
Spreads, contralateral	6
Tuberculous empyema	5
Mixed empyema	1
Bronchopleural fistula (early)	3
Bronchopleural fistula (after six months)	1
Uremia due to transfusion reaction	1
Total	27

the causation of amyloid disease). The cases of operative cardiac arrest were essentially due to very poor condition of the patient (2 were cases of acute pneumonic phthisis). There was also one case of reflex cardiac arrest in the older series, successfully treated by massage. In general, these causes of death were such as might be expected in any series of pulmonary resections irrespective of pathology. While they can probably be diminished by further improvements in selection, surgical technique, and postoperative care, it is doubtful if they can ever be entirely eliminated. There were eight such deaths in each series.

There has been considerable variation in the amount and duration of streptomycin therapy. However, we have basically given 1 Gm. daily for two weeks preoperatively and for three weeks after operation. In especially acute cases and those with excessive sputum, the dose has frequently been doubled and given for three to four weeks preoperatively and up to eight weeks after the resection. In no case has the daily adult dose been less than 1 Gm. In some individuals, of restricted financial capacity, streptomycin was begun just two to three days preoperatively and continued for an equal period postoperatively (two to three days). In no such instance did we feel that the patient was harmed, but we did limit this group to those with the more conservative surgical indications. We have repeatedly been able to confirm the observation of Ornstein[3] that there is a remarkable reduction in the amount of sputum and diminution in its purulent content during the two weeks preoperative streptomycin regime. While this sputum rarely becomes bacillus-free, the Gaffky count usually drops. It is our impression that these changes in the amount and character of the sputum remarkably reduce the chance of operative flooding of other portions of the bronchial tree with consequent reduction in the tendency to atelectasis and bronchiogenic spread. The relative absence of operative spreads (one case only, 1 per cent) in the streptomycin-treated group, as contrasted to the older group (15 per cent) certainly tends to bear this out. A factor of considerable importance in the prevention of postoperative atelectasis is attention to the tracheobronchial toilet. This includes the ordinary mechanisms of air passage evacuation such as encouragement of cough, carbon dioxide inhalation, transnasal transglottic tracheobronchial aspirations, bronchoscopy in the postoperative period, and occasionally tracheotomy for frequent aspiration. We are especially grateful for the help of Dr. J. A. Crellin of Philadelphia,[7] and Dr. Morris Pierson of Wilmington, Del.,[8] who have contributed to the setting up of the program of treatment which has worked so well in these cases.

We have felt that streptomycin therapy markedly reduced the postoperative incidence of tuberculous empyema except in those cases where a clinical bronchopleural fistula develops. This was especially evident in those cases where operative rupture of a caseous area led to gross contamination in the pleural space. Thus in 23 cases of operative gross pleural contamination in the prestreptomycin group, tuberculous empyema resulted in 13 instances (58 per cent). On the other hand in 18 cases in the streptomycin series only 3 empyemas resulted (18 per cent).

The protective effect of streptomycin also was very evident in cases of clinical tuberculous or mixed empyema, with or without bronchopleural fistula, which were treated by resection. While an attempt was usually made to remove the entire empyematous space, it was completely accomplished in only three instances, and pleural contamination occurred in two of those because of operative opening of the empyematous sac. Yet, pleural infection was demonstrable postoperatively in only 3 of the 12 cases (25 per cent). The rarity of chest wall infection and sinus development in these cases was most impressive, occurring in only two instances. One patient, who had had a fairly long (eight weeks) preoperative course of streptomycin, did develop a draining sinus which has existed about six months. She had had a wide bronchial fistula and pleural infection for more than one year preoperatively. At the time of operation, it was necessary to leave a large portion of the empyematous wall on the diaphragm and pericardium.

The occurrence of bronchopleural fistula in the early postoperative period is usually related to a failure of proper bronchial closure, although virulent pleural or mediastinal infection may well lead to sloughing of the suture line. This is probably aggravated by early severe coughing which applies extreme pressure to the suture line. We have observed a number of cases which have maintained a closed bronchus for three to five weeks postresection, then following an obliterative thoracoplasty the patient complained of blood spitting (brownish), and/or of extreme bulging of the softened chest wall. The bronchus apparently opened due to the force of coughing in the absence of the support of the intact costal cage. For such rupture to occur so long after the time of probable secure bronchial healing (fourteen days) suggests that normal healing had not taken place. Overholt[9] has shown that this is frequently due to ulceration in the bronchial stump. Since routine examination of the cut bronchus in resection cases reveals, according to Auerbach,[10] miliary tubercles in about 40 per cent of cases, it is not surprising that ulceration of the bronchial stump may occur. In view of the many favorable reports upon the use of streptomycin in endobronchial tuberculosis, it would seem probable that it should tend to prevent this stump ulceration, or to cause healing once such ulceration has occurred.

It is interesting to note that opening of the bronchus immediately after postresection thoracoplasty occurred in 4 cases in the prestreptomycin series and in one case of the streptomycin series. This latter case was the one of acute pneumonic phthisis with bilateralization in which multiple segmental resection was employed. We believe that the use of a double suture line, one of interrupted end sutures and one proximal mattress row, is of considerable protection against such an occurrence. We prefer stainless steel because of its inertness.

From this appraisal of our entire experience with pulmonary resection for tuberculosis, we have come to the conclusions that the beliefs first voiced upon the use of streptomycin in resection for pulmonary tuberculosis by Glover, Clagett, and Hinshaw[12] are essentially corroborated. Providing a

TABLE VI. BREAKDOWN OF CASES WITH PATIENTS LIVING

Results to date (nonstreptomycin group)		
Total	100	
Surgical deaths	27	
Deaths since operative period	10	
Living	63	
Known negatives (present)	55	(87.3% of living)
Unable to follow up	4	(6.3% of living)
Known positives	4	(6.3% of living)
Residual chest wall drainage	6	(10.5% of living)
Results to date (streptomycin group)		
Total	100	
Surgical deaths	16	
Deaths since operative period	0	
Living	84	
Known negatives	77	(91.5% of living)
Unable to follow up	0	
Known positives	2	(2⅜% of living)
Undetermined	5	(Very recent or no sputum determination available)
Residual chest wall drainage	4	(4⅜% of living)

previous course of streptomycin therapy has not rendered the patient bacteria streptomycin-fast, a definite suppression of the tuberculous process is produced during the preoperative therapy. The patient's disease then temporarily assumes a more chronic course, so that it can be subjected to surgery with a much greater margin of safety. In the treated group, the incidence of tuberculous operative spreads and flare-ups became practically nil. Infections of the pleura and chest wall were remarkably reduced in spite of the inclusion of 14 cases of empyema (with proved bronchopleural fistula in 12 cases) in the streptomycin-treated group.

The complications which are essentially due to the resection rather than to the tuberculosis were unchanged. While more difficult cases were frequently chosen for surgery in the streptomycin-treated group improvements in surgical technique rendered the nonspecific complications and mortality about the same.

We believe today that the mortality in pulmonary resection for tuberculosis can be set at any figure over 5 per cent, dependent upon the type of case selected for resection, and the choice between radical or conservative management must be left to the judgment of each individual clinic.

We cannot, of course, give an accurate idea of the relative incidence or freedom from late complications in these two series. However, there is nothing in our experience to suggest that the late results after resection surgery are essentially different from the late results in other forms of major surgery for pulmonary tuberculosis (Table VI).

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(See discussion on page 55.)

AN EVALUATION OF STREPTOMYCIN AS A PROTECTIVE AGENT IN PULMONARY RESECTION FOR TUBERCULOSIS

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THE first attempts to resect pulmonary tissue were made by Gluck,[1, 2] Schmid,[3, 4] Block,[5, 6] Biondi,[7] and Ziino[8] between the years 1881 and 1883. Tuffier[9] wrote of Gluck's and Schmid's extirpation of the lung in an animal and of an experiment by Biondi in which the lung of an experimental animal was inoculated with the tubercle bacillus and the resultant disease eradicated by pneumonectomy. Tuffier concluded: "In the first stroke, therefore, experimentation had achieved the end of its domain. All of those who succeeded these experimenters . . . have only confirmed their conclusions."

We are familiar with Block's first tragic attempt to perform a bilateral, apical resection for tuberculosis in 1881,[10] and with similar unsuccessful attempts by Ruggi[11] and Kroenlein.[12] Tuffier performed what is accepted as the first successful resection for tuberculosis in man in 1893. This was followed by the cases of Lowson in 1893[13] and Doyen in 1895.[14] Many surgeons attempted, successfully and unsuccessfully, to perform resections with varied technics until 1932, when Graham,[15] Lilienthal,[16] Freedlander,[17] and Rienhoff[18] reported their cases. The success of the latter group led to renewed efforts to eradicate tuberculosis by excision of the diseased tissue.

Thornton and Adams,[19] Dolley and Jones,[20] Behrend,[21] and Clagett[22] reviewed the literature up to 1944 and found that less than 90 cases of pulmonary resection for tuberculosis had been reported. We reviewed the American literature up to May, 1948, and found reported 616 cases of resection for pulmonary tuberculosis with a total mortality rate of 26 per cent and an operative mortality rate of 15 per cent in those cases in which the rate could be determined (Table I). The mortality rate for pneumonectomy was slightly more than twice that for lobectomy. Unfortunately, all surgeons have not reported in detail the causes of death nor the complications, such as spreads or exacerbations of tuberculosis, bronchial fistulas and empyemas, which are the main causes of the high mortality and morbidity accompanying these operations.

There was either a spread or an exacerbation of tuberculosis in 26 per cent of 456 cases (Table II). The incidence was higher following lobectomy (31 per cent) than following pneumonectomy 24 per cent). Empyema developed in 50 cases, or approximately 12 per cent of 421 resections (Table III).

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TABLE I. REVIEW OF AMERICAN LITERATURE OF PULMONARY RESECTIONS 1881-1948, MORTALITY RATE

AUTHORS	TOTAL NO. OF CASES	OVER-ALL NO. OF DEATHS	PER CENT OVER-ALL MORTALITY	NO. POST-OPERATIVE DEATHS 1ST 2 MO.	PER CENT MORTALITY 1ST 2 MO.
Composite of Thornton,[19] Dolley,[20] and Behrend[21]	85	34	40	Figures not obtained	Figures not obtained
Overholt[23]	196	46	24	27	14
Bailey[24, 25]	129	37	29	30	23
Sweet[26]	63	21	33	9	16
Janes[27]	32	6	19	2	6
Clagett[28]	29	4	14	2	7
Strieder[29]	23	4	17	3	13
Carr[30]	18	7	39	6	33
Maier and Klopstock[31]	16	1	6	1	6
Churchill[32]	9	1	11	0	0
Duncan[33]	5	0	0	0	0
Shenstone[34]	2	0	0	0	0
Total	607	161	26	80	15

In 31 of these, the empyema was tuberculous or mixed, while in the remaining 19 the empyema was pyogenic. Bronchial fistulas developed in 6 per cent, and all of these resulted in empyema.

In 1947 Overholt and his associates[23] reported that the operative mortality for both lobectomy and pneumonectomy was then approximately 5 per cent in patients who were considered reasonably good risks, and 43.6 per cent in pa-

TABLE II. REVIEW OF AMERICAN LITERATURE OF PULMONARY RESECTIONS 1934-1948, COMPILATION OF SPREADS AND/OR EXACERBATIONS

AUTHORS	NUMBER OF CASES	NUMBER OF SPREADS AND/OR EXACERBATIONS	PER CENT OF SPREADS AND/OR EXACERBATIONS
Overholt[23]	196	54	28
Bailey[24, 25]	80	15	19
Sweet[26]	63	20	32
Janes[27]	32	5	16
Clagett[28]	29	8	28
Strieder[29]	23	11	48
Maier[31]	16	1	6
Brantigan[35]	9	1	11
Duncan[33]	5	0	0
Churchill[32]	3	2	66
Total	456	117	26

TABLE III. REVIEW OF AMERICAN LITERATURE OF PULMONARY RESECTIONS 1934-1948, COMPILATION OF FISTULAS AND EMPYEMAS

AUTHORS	NUMBER OF CASES	NUMBER OF EMPYEMAS	PER CENT EMPYEMAS DEVELOPED	NO. OF FISTULAS	PER CENT FISTULAS DEVELOPED
Overholt[23]	196	22	11	12	6
Bailey[24, 25]	80	10	13	7	11
Sweet[26]	63	7	11	2	3
Janes[27]	32	6	19	4	13
Clagett[28]	29	3	10	2	7
Maier[31]	16	2	13	0	0
Duncan[33]	5	0	0	0	0
Total	421	50	12	27	6

tients who were very poor risks. Over a period of years Overholt has been able gradually to reduce the mortality rate and the incidence of spreads, bronchial fistulas, and empyemas. After he began to operate with the patient in the prone position, the results improved. His most recent report of results with use of the face-down position and local anesthesia stated that spreads or exacerbations occurred in 14 patients, or 13 per cent. Empyemas occurred in 6 per cent, and fistulas in 2 per cent of operations. Sputum was converted in 60 per cent of 104 patients in the series, while the average rate of sputum conversion reported in the literature is 50 per cent.

Prior to 1947 our experience with resection of the lung for tuberculosis had not been very extensive (Table IV). We had performed 2 pneumonectomies and 9 lobectomies for tuberculosis. Our operative mortality was 18 per cent, and the late mortality 18 per cent. Twenty-seven per cent of the patients developed spreads or exacerbations, and 55 per cent developed fistulas and empyemas. In 6, or 55 per cent, the sputum became negative. Our experience was probably worse than the average and we were not enthusiastic about resecting tuberculous lungs.

In June, 1946, the Veterans Administration Hospital at Oteen, N. C., was invited to participate in a co-operative study to evaluate the action of streptomycin in the treatment of tuberculosis. At first the use of streptomycin was confined to the treatment of chronic draining sinuses and selected cases of pulmonary tuberculosis. Results in this group have been reported by Brock, Parnell, and Moyer.[36, 37]

In January, 1947, this study was expanded to evaluate the prophylactic effect of streptomycin during various surgical procedures for tuberculosis. Shortly after this study was initiated at Oteen, streptomycin became available at the Western North Carolina Sanatorium at Black Mountain, N. C. We wish to report at this time our results of pulmonary resection for tuberculosis with the use of streptomycin at these two institutions.

The Streptomycin Committee established arbitrarily a dosage of 2 Gm. intramuscularly, divided into six doses daily, to be given one week before and two weeks after operation. This method was followed until October, 1947, at which time the dosage was cut to 1 Gm. daily, divided into two doses given at twelve-hour intervals begun one week before and continued for two weeks after operation. The reduction in amount of streptomycin was made because of the serious toxic effects and the development of resistance to the drug noted in the study on pulmonary patients being conducted simultaneously. It was desired, also, to establish the minimum effective dosage of this new therapeutic agent. So far as we can judge, the smaller dosage has been as effective as the larger, and no toxic reactions have resulted from the three weeks' course of treatment with either dosage.

It was felt that the technique of pulmonary resection was fairly well standardized and that the experience of many surgeons demonstrated that the mortality and morbidity rate were almost prohibitive. It was agreed that these reports offered a sufficient background of experience with which to

TABLE IV. OUR RESECTIONS PRIOR TO USE OF STREPTOMYCIN

LOCATION	NO. OF PATIENTS	EARLY DEATHS		LATE DEATHS		EMPYEMAS		FISTULAS		SPREADS AND/OR EXACERBATIONS		POSITIVE SPUTA		NEGATIVE SPUTA		CONTRALATERAL DISEASE PRIOR TO SURGERY	
		NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
Oteen	6	1	17	0	0	2	33	2	33	2	33	1	17	4	67	0	0
WNC Sanatorium	5	1	20	2	40	4	80	4	80	1	20	2	40	2	40	1	20
Total	11	2	18	2	18	6	55	6	55	3	27	3	27	6	55	1	9

compare the streptomycin-treated cases. For these reasons it was not deemed practical nor fair to the patients to run a control group of resections without the use of streptomycin. A further condition of the study was that indications for operation should not vary from those in use at the respective clinics before streptomycin was used.

The criteria which we have accepted as indications for resection are as follows:

1. Residual cavity after thoracoplasty. Thirty-eight of the 85 resections, or 45 per cent, were done for this reason. Of these, 35 per cent showed endobronchial disease.

2. Failure of more conservative methods of collapse therapy such as pneumothorax and pneumoperitoneum; 13 cases, or 15 per cent of the total number were in this category. Five of these patients had endobronchial disease; 5 had a hilar or a basal cavity.

3. Tuberculous bronchiectasis. Thirteen operations were done for this reason.

4. Destroyed lung. Pneumonectomy was performed under this indication in 10 cases.

5. As an elective operation in place of thoracoplasty; 7 patients were operated upon for this reason. None had demonstrable endobronchial disease.

6. Severe endobronchial disease with stenosis. Three operations, or 4 per cent of the total number, were performed for this lesion.

7. Tuberculoma; one operation.

In 40 per cent of all resections, a preoperative bronchoscopic examination revealed endobronchial disease.

All of these patients were operated upon under intratracheal anesthesia by the closed circle anesthesia technique introduced by Sword[38] in 1928. Cyclopropane, ethylene, or ether was employed; occasionally curare was administered if the motion of the diaphragm proved troublesome during operation. Throughout the operation the anesthetist kept the tracheobronchial tree free of sputum.

At Oteen all patients were operated upon in the prone or Overholt position; at the State Sanatorium, because of lack of equipment, all operations were done with the patient in the lateral position. Streptomycin was given intramuscularly, beginning one week before and continued for two weeks after operation. It was not instilled into the pleural space. Penicillin was instilled into the pleural space before closure of the pleural cavity and was given parenterally in adequate doses following operation. Undoubtedly, this measure has played an important part in the prevention of pyogenic infection of the wound and the pleura.

All operations, except one in which technical difficulties made the use of a tourniquet necessary, were done by the individual ligation technique. In this patient the bronchi were closed individually and covered with pleura, but later a fistula and empyema developed. In all cases the bronchus was closed with interrupted sutures of fine silk or fine stainless steel wire and

covered with a pleural flap, or allowed to retract so that the mediastinal pleura could be sutured over it. The vessels were ligated individually with heavy silk reinforced with a transfixion suture of medium silk.

In all patients treated by pneumonectomy, the chest cavity was drained for forty-eight hours. In the lobectomy cases, drainage was instituted and suction applied until the remaining lobes had re-expanded. Adequate amounts of blood were given during the operation, an average of 2,000 c.c. per patient. Blood was given postoperatively as indicated. All patients were given oxygen as required through an intranasal catheter.

A few patients who developed atelectasis of varying degree were treated promptly by bronchoscopic aspiration.

Seventy-four resections were done on 74 patients between January, 1947, and May 1, 1948, with the use of streptomycin as a prophylactic agent. Of these, 35 were lobectomies and 39 pneumonectomies. One of the 35 lobectomy patients (Table V) died from hemorrhage shortly after operation, a mortality rate of 2.9 per cent. There were no late deaths, and there are no patients who are not doing well at present. One patient developed a fistula with empyema and he is being treated by thoracentesis combined with thoracoplasty. A spread of the disease occurred in one patient, an unco-operative man, who developed a small contralateral area of pneumonitis six weeks after operation. This cleared in one month with streptomycin therapy and the sputum remained negative. One patient developed a progression of the disease sixteen months after surgery and was readmitted to the hospital. Another patient developed tuberculous meningitis about five weeks after lobectomy, and has apparently been cured by the administration of streptomycin. In 92 per cent of the 35 patients the sputum became converted. Contralateral disease was present in 34 per cent, but was considered quiescent at the time of operation. Our immediate results are most gratifying, but we realize that as time goes on, there will probably be reactivation of the disease in some of the patients.

Of the 39 pneumonectomy patients, 5 died, an operative mortality of 13 per cent (Table VI). One patient died of uncontrollable hemorrhage on the operating table; one died several days after operation from the effects of cerebral anoxia caused by cardiac arrest, the result of severe hemorrhage on the table. One died of right ventricular failure seventeen days postoperative. One died of a contralateral spread of the disease. It is interesting to note that this patient had been given 2 Gm. of streptomycin daily for seven months before admission for operation. Undoubtedly the organisms had become resistant to streptomycin, and the patient lost the protective value of the drug. A fifth death occurred in a diabetic patient ten days after operation, immediately following an attempted thoracentesis. A post-mortem examination failed to reveal any satisfactory explanation for death.

Three patients, or 8 per cent, developed fistulas and empyemas. These were treated by thoracotomy and thoracoplasty. In 1 a tuberculous wound infection developed after thoracoplasty. In 2, or 5 per cent, spreads or ex-

TABLE V. OUR LOBECTOMY RESULTS USING STREPTOMYCIN

LOCATION	NO. OF PATIENTS	EARLY DEATHS		LATE DEATHS		EMPYEMAS		FISTULAS		SPREADS AND/OR EXACERBATIONS		POSITIVE SPUTA		NEGATIVE SPUTA		CONTRALATERAL DISEASE PRIOR TO SURGERY	
		NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
Oteen	33	1	3	0	0	1	3	1	3	1	3	2	6	30	90	11	33
W.N.C. Sanatorium	2	0	0	0	0	0	0	0	0	0	0	0	0	2	100	1	50
Total	35	1	2.9	0	0	1	2.9	1	2.9	1	2.9	2	5.7	32	92	12	34

TABLE VI. OUR PNEUMONECTOMY RESULTS USING STREPTOMYCIN

LOCATION	NO. OF PATIENTS	EARLY DEATHS		LATE DEATHS		EMPYEMAS		FISTULAS		SPREADS AND/OR EXACERBATIONS		POSITIVE SPUTA		NEGATIVE SPUTA		CONTRALATERAL DISEASE PRIOR TO SURGERY	
		NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
Oteen	27	2	7	0	0	3	11	3	11	0	0	1	4	24	89	6	22
W.N.C. Sanatorium	12	3	25	0	0	0	0	0	0	2	17	2	17	8	67	7	58
Total	39	5	13	0	0	3	8	3	8	2	5	3	8	32	82	13	33

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acerbations occurred. One of these patients died, as reported previously; the other recovered with the continued use of streptomycin.

In 32, or 82 per cent of the pneumonectomy group, the sputum became negative. This is rather remarkable, inasmuch as in 33 per cent contralateral disease was present, and in 17 per cent it was considered to be active at the time of operation. There have been no late spreads or deaths in this group. Here again we realize that eventually some of these patients will die of tuberculosis.

The 74 cases of resection of the lung with streptomycin are listed in Table VII. The operative mortality is 8.1 per cent. There have been no late deaths to date. In 5 per cent empyemas developed and were considered to be the result of fistulas. These were assumed to be tuberculous, even though the organisms could not be demonstrated in all instances. In 5 per cent bronchial fistulas developed, probably from failure to maintain a tight closure of the bronchus. This fault in technique should occur with less frequency in the future. Spreads followed 4 per cent of the operations. There have been no deep tuberculous wound infections and only a few minor wound infections following resection, and no late spreads or empyemas to date, but there has been progression of disease in one patient sixteen months after operation.

In our cases the mortality rate has been reduced from 36 per cent to 8.1 per cent; the rate of spreads from 27 per cent to 4 per cent; the rate of fistulas and empyemas from 55 per cent to 5 per cent; and the rate of sputum conversion has risen from 58 per cent to 87 per cent. Ninety-two per cent of the living patients have a negative sputum.

We feel that streptomycin has been the major factor in lowering the mortality and morbidity rate in our experience. We frankly admit, however, that at the time we began the use of streptomycin we had not had a large experience with the operation of pulmonary resection, particularly in tuberculosis. We had not mastered the individual ligation technique. It is our opinion that improvement in operative technique and skill, improved methods of anesthesia, the use of adequate amounts of blood, improvement in preoperative and postoperative care, and the meticulous attention to details throughout the entire period of treatment have contributed materially to the improvement in results.

We believe that adoption of the Overholt position has been a definite factor in the reduction of spreads. In patients operated upon at the Western North Carolina Sanatorium where the lateral position is used, there was an incidence of 14 per cent of spreads. At Oteen, where the Overhold position is used, the incidence of spreads was 1.6 per cent.

The fact that no patient developed serious wound infection and none developed empyema, except in cases with bronchial fistulas, proves to us that protection against gram-positive organisms is afforded by penicillin and against gram-negative organisms and the tubercle bacillus by streptomycin. In 25 per cent of the cases, particularly in cases of resection after thoracoplasty, gross contamination of the pleural cavity has occurred due to rupture

TABLE VII. OUR TOTAL RESECTION RESULTS USING STREPTOMYCIN

LOCATION	NO. OF PATIENTS	EARLY DEATHS		LATE DEATHS		EMPYEMAS		FISTULAS		SPREADS AND/OR EXACERBATIONS		POSITIVE SPUTA		NEGATIVE SPUTA		CONTRALATERAL DISEASE PRIOR TO SURGERY	
		NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
Oteen	60	3	5	0	0	4	7	4	7	1	1.5	3	5	54	90	17	35
W.N.C. Sanatorium	14	3	21	0	0	0	0	0	0	2	14	2	14	10	72	8	57
Total	74	6	8.1	0	0	4	5	4	5	3	4	5	7	64	87	25	34

of the cavity. We have not been able consistently to free these densely adherent lungs without a rupture into the cavity. Yet in no instance has this accident resulted in empyema or wound infection.

We are of the opinion that streptomycin is a suppressive or bacteriostatic agent of proved value against the tubercle bacillus. It is not a cure for tuberculosis. In certain types of cases, however, it has proved to be of inestimable value in controlling the disease. It is too early for any one to attempt to assess its value in the treatment of tuberculosis. This cannot be done until several years have elapsed. From our clinical experience we feel that its chief place in the treatment of tuberculosis is as an adjunct to establish collapse procedures. Streptomycin has made it possible for us to perform a lobectomy or a pneumonectomy for tuberculosis with a low morbidity and mortality rate and with excellent early results.

If late results after pulmonary resection prove to be as gratifying as those after thoracoplasty, we are confident that the indications for pulmonary resection will be greatly extended.

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DISCUSSION ON "STREPTOMYCIN AS AN ADJUNCT IN SURGICAL TREATMENT OF PULMONARY TUBERCULOSIS" BY DR. DANIEL A. MULVIHILL, DR. LAURENCE MISCALL, DR. ROBERT KLOPSTOCK, AND DR. JOSEPH BITSACK;* "THE ROLE OF STREPTOMYCIN IN THE SURGERY OF PULMONARY TUBERCULOSIS" BY DR. PAUL T. CHAPMAN, DR. E. J. O'BRIEN, DR. PAUL V. O'ROURKE, AND DR. BRUCE DOUGLAS;† "EXPERIMENTAL AND CLINICAL STUDIES OF THE ROLE OF STREPTOMYCIN IN THE PLEURAL CAVITY" BY DR. EDWARD J. BEATTIE, JR., DR. BRIAN BLADES, AND DR. CHARLES HORTON;‡ "COMPARISON OF RESULTS IN TWO HUNDRED CONSECUTIVE RESECTIONS FOR PULMONARY TUBERCULOSIS" BY DR. CHARLES P. BAILEY, DR. ROBERT P. GLOVER, AND DR. THOMAS J. E. O'NEILL;§ AND "AN EVALUATION OF STREPTOMYCIN AS A PROTECTIVE AGENT IN PULMONARY RESECTION FOR TUBERCULOSIS" BY DR. JULIAN A. MOORE, DR. JAMES D. MURPHY, AND DR. PARKER D. ELROD.

DR. RICHARD H. SWEET, Boston.—I would like to bring forth at least one dissenting voice about something that has been mentioned several times, namely, the use of the face-down position, because as I glanced hastily at Dr. Moore's slides it looked to me as though my results—although it was of course a much smaller series—were not very much different from those of Dr. Overholt and I have always used the standard position. I would like to tell you a story which I believe is pertinent. About two years ago Dr. John Alexander came to Boston to visit both Dr. Overholt and me. He spent one morning watching Dr. Overholt use the face-down position, and then came down and had luncheon with us at Massachusetts General Hospital. He said that the face-down position had been used in sixty-nine cases with only four cases of postoperative spread of the disease. Dr. Henry Beecher, who was present, said, "That is of great interest, because some years ago we pub-

*See page 1 for article by Mulvihill, Miscall, Klopstock, and Bitsack.
†See page 15 for article by Chapman, O'Brien, O'Rourke, and Douglas.
‡See page 25 for article by Beattie, Jr., Blades, and Horton.
§See page 36 for article by Bailey, Glover, and O'Neill.

lished the results on a series of 149 cases, with eight so-called spreads to the other side.'' Not being much of a mathematician, it seemed to me that the percentages were essentially the same.

It seems obvious from listening to these excellent papers today, that streptomycin is a great help in getting patients through the operation, but I wonder just where its place lies in the subsequent course. Therefore, I wondered if those of you who heard the report two years ago based upon the nonstreptomycin series would be interested to know what has happened to that small group. At that time out of the lobectomy group of 27 cases we had 13 patients who were perfectly well so far as we could tell. In the subsequent years 6 have remained well continuously; 7, however, developed reactivation at some time. Two of those were treated with streptomycin and apparently were restored to a comparatively normal state. Twelve of the original 14 are well today. Of the 17 patients in the original pneumonectomy group reported as well 2 years ago, 14 are still well. That is, without streptomycin.

DR. HERBERT C. MAIER, New York.—There are two points that I should like to discuss. First, in relation to streptomycin and pleural absorption. I think it is important to bear in mind the degree of vascularity of the pleura, as well as the extent of pleural thickening or scarring in interpreting absorption studies. From the pathology as described in the cases studied, it would seem that considerable vascularity of the pleura was present. I wonder, therefore, if the pleura is thickened and relatively avascular, whether the results of similar studies would not show quite a different absorption rate.

The other point that I should like to discuss is the importance of very careful maintenance of the cardiorespiratory physiology at the optimum level during operation and in the early postoperative period after pulmonary resection. In our experience, deaths primarily from cardiorespiratory dysfunction have been less than 1 per cent, irrespective of the type of lesion for which the resection was performed. In the early cases of our series for tuberculosis, spread of the disease was the chief difficulty. During the last two years I have had one postoperative death in those patients who had pulmonary resection for tuberculosis. I think that when pneumonectomy is done following thoracoplasty a very careful adjustment of the intrapleural pressure and position of the mediastinum is particularly important because of the small space that remains. A slight increase in the amount of air trapped in that space may lead to what is called cardiorespiratory dysfunction, but which actually is primarily a disturbance due to mechanical factors. I think that more careful attention postoperatively to the position of the mediastinum as well as being certain that the patient is never anoxic during the operative procedure will reduce morbidity and mortality. I wonder whether studies have been done on the face-down position on the operating table to determine whether any anoxia occurs, because we must keep our patients well oxygenated as well as avoid spread of secretion to the other side. I think such factors may account for some of the differences of opinion and differences in results.

COL. J. H. FORSEE, Denver.—In a rather extensive experience in the use of streptomycin at Fitzsimons General Hospital, and with adequate quantities of this drug available, we have come to define the indications for its use essentially as follows: (1) As a selective measure in which it was believed that collapse therapy would not be necessary to arrest the disease; this has included a very small percentage of patients. (2) To improve operability or to convert an unsatisfactory operative risk in need of surgery into a satisfactory risk. (3) As Dr. O'Brien said, as a prophylactic. We have used streptomycin preoperatively, during operation, and after operation, in all patients coming to thoracoplasty during the past eighteen months. Prophylactically it has been, we believe, of particular value in those patients with large cavities who were otherwise good chronic risks, but in whom the danger of spread of the disease has been considerable. We think the spread of the disease has been decreased by the use of streptomycin. In fact, we have encountered spread of the disease in only one patient among a consecutive series of 78 subjected to thoracoplasty, in whom 232 operations were performed. (4) We have used it for the relief of certain distressing symptoms, such as tuberculous cystitis or tuberculous laryngitis, in chronic far-advanced diseases.

Those patients whom we have felt we have converted from an unsatisfactory risk into a satisfactory one, and in whom we have carried out thoracoplasty, constitute approximately 23 per cent in a total of 78 patients, treated by thoracoplasty, with the use of streptomycin. A few illustrative cases in the latter group will be presented.

CASE 1.—A 29-year-old Negro soldier was hospitalized May 15, 1947, because of a temperature of 102° F. and a mildly productive cough. He was transferred to Fitzsimons General Hospital May 31, 1947, at which time sputum was positive for tuberculosis and Kahn reaction was positive. Chest roentgenogram revealed an exudative infiltration throughout the right lung with large (6 cm.) and smaller cavitation in the right upper lobe and evidence of an extension in the left lower and right lower lung fields. Streptomycin, 2 Gm. daily, was given from June 13 to October 14. In November a tuberculous laryngitis and an ulcerative endobronchial tuberculosis of the right upper lobe orifice was diagnosed. In November the patient was afebrile, sedimentation rate was 25/60, and the exudative infiltration bilaterally had cleared considerably but the upper lobe cavity on the right remained. On Dec. 4, 1947, streptomycin therapy, 1 Gm. daily, was again started. A seven-rib thoracoplasty on the right was carried out between Dec. 18, 1947, and Jan. 30, 1948. Streptomycin was discontinued March 5, 1948, after he had received 332 Gm. over a period of 209 days. The sputum production is now nil and negative on smear and culture. X-ray examination of the chest does not reveal evidence of cavitation. Within eight months from the time of onset of illness, thoracoplasty had been completed.

CASE 2.—A 20-year-old Negro soldier was hospitalized Nov. 10, 1945, because of chest pain and cough. X-ray examination of the chest revealed a shadow of infiltration in the right mid-lung field and sputum was positive for acid-fast bacilli. On Dec. 11, 1945, he suffered a spontaneous pneumothorax on the right, associated with a temperature of 104° F. He gradually improved and was admitted to Fitzsimons General Hospital March 31, 1946. At this time he had lost thirty pounds in weight, was dyspneic to a severe degree, and daily temperature averaged 102° F. The patient was placed on streptomycin, 2 Gm. daily, from June 18 to Oct. 18, 1946. By January, 1947, there had been considerable clearing of the lesions but a cavity remained in the right upper lobe. The patient had received 216 Gm. of streptomycin, 2 Gm. daily, and ten days later a first stage thoracoplasty was carried out. A four-stage ten-rib thoracoplasty was completed March 7, 1947, and streptomycin was discontinued April 1, 1947. He was given 152 Gm. of streptomycin in the second course and a total dosage of 368 Gm. A follow-up letter from Veterans Administration stated sputum examination and gastric washings for tubercle bacilli have been repeatedly negative, general condition is good, and the clinical course symptom-free. He had been a severe disciplinary problem and was discharged from the VA hospital Jan. 28, 1948. Sixteen months elapsed from the onset of the disease until the completion of thoracoplasty, and he was discharged from the hospital ten months after thoracoplasty.

CASE 3.—A 25-year-old white soldier was well until April, 1947, when he had an acute onset of fever, chills, cough, night sweats, and malaise. A roentgenogram of the chest revealed an exudative infiltration throughout the left lung with cavitation of the left upper lobe, and the sputum was positive for acid-fast bacilli. He was admitted to Fitzsimons General Hospital June 22, 1947, at which time he was toxic, with daily temperatures of 100 to 101° F., and expectoration of ¼ cupful of sputum daily. On July 7, 1947, he was started on streptomycin, 2 Gm. daily. After four months of such therapy there had been rather marked resolution of the exudative element as noted on roentgenograms, temperature was normal, and sputum production had decreased to 10 c.c. per day. On November 19 he was started on a second course of streptomycin prior to thoracoplasty. Between Nov. 24, 1947, and Jan. 26, 1948, a four-stage eight-rib thoracoplasty had been performed. Streptomycin was discontinued after 228 days of therapy and a total dosage of 456 Gm. The postoperative course after each operation was uneventful and in April, 1948, the sputum was negative with no evidence of cavitation noted on x-ray examination. From the time of onset of illness to completion of thoracoplasty, nine months had elapsed.

We believe that streptomycin has its best use in preparing patients for thoracoplasty. We believe, as Dr. Sweet has indicated, that lobectomy and pneumonectomy are very important, but we would like to reserve pulmonary resection, in general, for use in cases in which the cavities have failed to close after thoracoplasty.

DR. EDWIN J. GRACE, Brooklyn.—Fleming and Florey at the outset of their vital contributions to the clinical use of penicillin brought out one very important fact, and it is a matter of great regret that many Americans have forgotten this fundamental principle, namely, direct topical therapy. Anything that can enhance the efficiency of topical treatment is a very significant adjunct to antibiotic therapy. Enough experience has been gained to show that the development of resistant bacterial strains is today a very formidable clinical problem. (Slide.) The experimental evidence noted here shows how this dangerous phenomenon of bacterial resistance may be prevented. The bacteriologic phase of our work on the prevention of antibiotic-resistant organisms was done by my colleague, Dr. Vernon Bryson.

If a broth culture of *Staphylococcus aureus* is inoculated with approximately 100,000 cells per cubic centimeter, the number is found at the end of six hours to be 27,000,000 per cubic centimeter, and after a twenty-four hour interval of incubation the final count is approximately 150,000,000. When an equivalent number of cells is grown in aerosol O.T. (dioctyl ester of sodium sulfosuccinate), 1:25,000, the number drops below the inoculum size but eventually at twenty-four hours a titer of 13,000,000 organisms per cubic centimeter is found. When growth is in the presence of .02 units per cubic centimeter of penicillin the twenty-four hour viable count is 83,000,000 bacteria per cubic centimeter, most of which can be shown to be penicillin-resistant.

Now a most interesting and clinically significant observation is made when we combine the detergent (aerosol O.T., 1:25,000) and penicillin, .02 units per cubic centimeter. The inoculum of 100,000 cells now falls to 690 per cubic centimeter in six hours and at twenty-four hours no viable cells remain.

This combination of penicillin and the detergent in which we obtain such a high degree of efficiency in the destruction of pathogens is referred to as synergism. The process of bacterial destruction is beyond the additative effect of the two therapeutic agents. We believe that in the application of basic genetic principles involved in the origin of bacterial resistance we may substantially diminish the frequency of clinical problems arising as a result of drug fastness in microorganisms.

In some of the papers presented this morning the speakers refer to patients returning for follow-up after initially good results. What really may be happening is the initial destruction of drug-sensitive organisms as a result of selective elimination by the antibiotic. The patient is then left with the clinically refractory "resistant strains." (Slides.) As the slide demonstrates, when we combine the antibiotic and the detergent we destroy all organisms. Although this experiment was run for twenty-four hours from other data we believe all bacteria were destroyed in between six to twelve hours. With topical antibiotic therapy the clinical question of penetration of tissue is vital in order to effect good topical therapy. Consequently, we have on this second slide a demonstration of efficiency of the detergent in penetrating the femur of a rabbit.

As a control, .3 c.c. of a 1 per cent fast green in saline is injected into the lower end of the bone. The penetration is very limited. However, if this same quantity of dye is dissolved in a detergent, 1:1000 aerosol O.T., and injected in the same manner, the femur is more effectively penetrated, perhaps in part because of the lipophilic properties of the wetting agent. Using this principle clinically in many otherwise hopeless cases of suppurative diseases of the lung including pulmonary tuberculosis, we have effected a cure by the very conservative techniques of topical antibiotic therapy.

The added experimental and clinical evidence we have acquired following a discussion of a paper on suppurative diseases of the lung at the St. Louis meeting, and from the papers read this morning on the use of streptomycin alone, either locally or parenterally, strongly convinces me that antibiotics with detergents topically, or as an aerosol mist, most certainly should be considered the method of choice before any form of surgical intervention.

We have never exceeded 50 to 60 Gm. of streptomycin in these cases and consequently had no permanent eighth nerve damage. Our experience in thoracic infections now exceeds fifty cases.

Our profession should realize that with the advent of antibiotic therapy a new era of medicine has dawned. All treatment for infectious diseases, therefore, should be promptly re-evaluated in strict accordance with the original concept of topical therapy.

DR. LOUIS R. DAVIDSON, New York.—My remarks will be confined to a group of patients operated upon at Sea View Hospital during the year 1947. These patients received streptomycin both preoperatively and postoperatively. Unfortunately, I am not in a position to compare a similar series of cases in which streptomycin was not given during the same period. Seventy-six patients had major surgery. There were 59 excisional cases; 44 pneumonectomies, 13 lobectomies, and 2 lobectomies with segmental resection. Of these 59 cases, 51 patients underwent postexcisional thoracoplasty. Fifteen patients underwent thoracoplasty procedures in stages; 1 patient had a thoracoplasty in stages with a Monaldi intubation. Finally, 1 patient had a revision of a Schede operation. Streptomycin was usually administered for a period of two to three weeks prior to surgery. (1) Postexcisional thoracoplasty patients, therefore, received the drug for three months. (2) Those patients having a conventional stage thoracoplasty received the drug for a period of one and one-half months. (3) Those patients who underwent a muscle splitting thoracoplasty received the drug for two months.

Penicillin.—All patients in this series received penicillin. The drug is usually given two to three days preoperatively and was continued until the temperature returned to normal.

Resistance.—Unfortunately, during the year 1947, no studies of the resistance of the tubercle bacillus were made. Most reports indicate that resistance to streptomycin occurs as early as the thirtieth day. Most of our patients received the major portion of their surgery during this period when the organism was sensitive to streptomycin.

Effects on Sputum.—It was noted that 35 patients had a reduction in both cough and the amount of sputum. In addition, there seemed to be a thickening of the sputum.

Effect on Sinuses.—Streptomycin was used in only two cases. Healing occurred in one month in both. No conclusions could be drawn; however, it will be interesting to follow these cases and note if the wounds remain intact.

Effects on Wounds.—These 76 patients underwent 165 operative procedures; wound complications were encountered in 14 cases. The tubercle bacillus was found on smear or culture in 7 cases. One must recognize that antibiotics have their limitations. It may not be amiss at this point to indicate that intelligent surgical technique is still necessary.

Toxicity.—The reactions noted were transient and were not of such a nature that the drug had to be discontinued; the most frequently encountered reaction was vertigo. Twenty-four patients revealed some reaction. As a rule the vertigo disappeared even though the therapy was continued. In a few cases the vertigo persisted and, obviously, the streptomycin was discontinued. Some of the patients related that relief was obtained by the use of Benadryl. This was not definitely controlled. As a result, therefore, no accurate figures can be advanced. Tinnitus occurred in 6 cases; dermatoses appeared in 7 cases; pruritis in 2 cases—itching was relieved by the administration of Benadryl; nausea and vomiting occurred in 3 cases; transient headaches were manifest in 3 cases. Three patients had reactions sufficiently severe to require discontinuance of the drug.

Postoperative Spread.—Because of varying criteria, it was finally decided to include in this group only cases in which the x-ray findings persisted beyond the immediate postoperative period. Five patients had a postoperative spread. Four of them, however, had negative sputum. In cases of mixed infection tuberculous empyema there has been performed at Sea View Hospital 15 cases of complete pleurectomy and pneumonectomy. It seems to us that streptomycin in these cases plays a spectacular and convincing role. This antibiotic, it must be stressed, is an adjunct only. It still must face the test of time.

DR. N. J. WILSON, Boston.—I should like to present the figures from Dr. Overholt's Clinic for 1947 for the purpose of emphasizing some of the points brought out in the papers.

It seems that streptomycin without any question is a very valuable antibiotic and has made surgery upon the tuberculous patient, especially resection, much safer. We now use streptomycin routinely in both the pre- and postoperative periods in pulmonary resection. Just which patients should receive streptomycin for other procedures is not absolutely clear to us as yet. For instance, in the thoracoplasty series we have used it only in preparing the substandard risks and have done the standard risks without streptomycin.

In 1947, there were 48 pulmonary resections performed, 39 pneumonectomies, and 9 lobectomies. One contralateral spread and one bronchial stump ulcer in the pneumonectomy series and one contralateral spread in the lobectomy series have been the only tuberculous complications in this group. Only one patient died of tuberculous infection. This represents a definite improvement as compared with previous years, in spite of the fact that most of these patients had inadequate streptomycin according to present concepts. These statistics gain significance when tuberculous infection as a cause of death following resection prior to 1947 is analyzed as follows:

In the entire series of 276 resections performed between 1934 and Jan. 1, 1948, there have been 43 infectious deaths including postoperative and late; 17 occurred postoperatively, and 26 late. The significant thing from the standpoint of streptomycin is that all these deaths except seven have been related to a postoperative complication. In other words, only 7 patients have died of progression of old disease. If streptomycin can reduce these postoperative complications, which it seems to do, then the future of these people seems to be very much improved.

DR. JEROME R. HEAD, Chicago.—Two factors have limited the use of streptomycin and prevented an unbiased estimation of its value. These are the unknown factor of complications and the high cost of the drug. In most public institutions lack of funds has made it impossible to supply the drug for every patient, and fear of complications has demanded caution in its use. In order, therefore, to discourage the general demand for it, it has been necessary to exaggerate its dangers and to maintain that it was of value only in particular types of cases. In most larger institutions streptomycin boards have been established to observe its effects and to choose the cases in which it is to be used. One cannot escape the feeling that the conclusions reached by these boards as to indications, dosage, and interval between doses have been seriously influenced by the monetary factor. Very often the members of the boards, even without a basis of experience, became astoundingly adept in telling what case streptomycin would help and what case it would not help, and also in telling from the roentgenogram precisely what type of lesion each shadow represented.

I have never been able to do either of these things. I felt sure, and am still convinced, that with so new a drug and so complicated a disease, a priori judgments are unjustified. One is warranted in saying that streptomycin will or will not benefit any certain case only after he has tried it on this particular case and has determined by experience that it has helped or has not helped.

For the past year we have used streptomycin in every case. The results have been generally good and generally unpredictable. Whereas over past years in our sanatorium we have had an average of 25 deaths a year, in 1947 there were only 9 deaths, and in the first six months of 1948 there has been but 1 death.

Dr. O'Brien said that streptomycin has revolutionized the surgical treatment of tuberculosis. It has done the same thing for the medical management. We should all realize that no one of us any longer knows anything about the amount of rest that is needed or about the indications for collapse. All of the old formulas and equations which we have developed so laboriously from experience have been made valueless because there has been injected into them this unknown factor. We do not know to what extent we can shorten the period of bed rest or in what cases we can dispense with collapse. We must start over again and build new formulas containing this at present unknown factor. For a certain type of case the old formula was: Six months bed rest plus four years pneumothorax = cure. Today that formula is: ? months bed rest plus ? (? years pneumothorax) plus streptomycin = cure. It will take some time to become reoriented.

DR. CAMERON HAIGHT, Ann Arbor.—The indications for treatment in pulmonary tuberculosis are changing as a result of the use of streptomycin. In view of the limited time that streptomycin has been available, it is somewhat difficult at present to crystallize the absolute indications for some of the types of treatment. This situation pertains to pulmonary resection, about which I would like to make a few remarks concerning indications and immediate results in patients who have received streptomycin.

There are at present strict indications for pulmonary resection with which most surgeons are in agreement. These consist of residual cavities after thoracoplasty, post-tuberculous bronchiectasis with positive sputum, severe bronchostenosis, and tuberculomas. The patients with acute exudative disease constitute a different indication, inasmuch as other methods of treatment are usually effective. At the University of Michigan Hospital we have had no experience with resection in patients with acute exudative disease.

During the past fifteen months streptomycin has been used in conjunction with pulmonary resection in almost all of our cases. Our results have shown a distinct improvement in comparison with earlier results. We feel, however, that streptomycin has not been the sole reason for the improved results, but rather that well-chosen indications and improved technique have also played an important part. In this period of fifteen months, pulmonary resection has been done for 50 consecutive patients, all of whom presented strict indications. It is too soon to know the late results, but the early results have been encouraging. No deaths have occurred. One spread developed as a result of operation in a patient with active tuberculous bronchitis with stenosis and an inflation cavity containing retained secretions. Two late spreads occurred, but the spreads in all three cases have cleared satisfactorily. One patient developed an empyema and bronchial fistula.

Streptomycin provides an adjunct which helps particularly, as mentioned this morning, in the preparation of patients for operation. It is distinctly useful after operation should complications occur. More especially, however, we feel that the proper choice of cases is the important consideration at the present moment in the treatment of pulmonary tuberculosis by resection.

DR. ROBERT G. BLOCH, Chicago.—I should like to remark on the dosage of streptomycin. There has been a recent tendency to decrease the dosage to a fraction of what was prescribed during the early period of this therapy. The essential reasons for this have been the great expense of the drug and the toxic manifestations resulting from the larger doses. It is possible that the smaller doses such as ½ Gm. daily are sufficient for all therapeutic purposes; however, as yet no scientific proof for this has been offered, but we do know that not only do variants of the tubercle bacilli present in most patients become streptomycin-resistant under therapy but that some variants are naturally resistant before the beginning of treatment. The reactivations of disease after what seems to have been successful streptomycin therapy probably result from the growing out of these resistant variants. As long as there is a posibility that larger doses such as 2 Gm. daily may vigorously dispose of some of the organisms which under smaller dosage would become resistant, I recommend caution in reducing the dosage, at least during the first few weeks of treatment.

Like some others we have lately been experimenting with para-aminosalicylic acid (PAS) which was found by Lehmann in Sweden to be bacteriostatic for the tubercle bacillus. While this drug alone has a somewhat lesser effect than streptomycin alone, the two drugs given in combination have exerted a powerful bacteriostatic effect in vitro and in vivo (in guinea pigs). Further experiments and trials will be needed to establish the validity of the results so far obtained.

DR. LAURENCE MISCALL, New York.—Dr. Churchill and Dr. Klopstock, in an original paper, pointed out the desirability of the straightforward approach with primary resection in the treatment of pulmonary tuberculosis. After Dr. Klopstock left Dr. Churchill he came to Triboro Hospital where he has been working for approximately five years. In the last year we have followed their concept of the application of excisional therapy and have tried to select a continuous series of cases which seemed suitable for primary lobectomy

or pneumonectomy. With streptomycin given preoperatively for that period during which the patient continues to improve, and followed routinely by ninety days of postoperative treatment, we have in the last seven months completed 31 consecutive resections, 27 lobectomies and 4 pneumonectomies. There have been no deaths nor postoperative spreads. Two fistulas which occurred were promptly closed by muscle transplant. I think they probably represent errors in operative technique. All patients are doing well, but the long-term result I cannot predict. I think that in all discussion of excisional therapy one point can be made, and I believe it runs through all the papers. Since primary resection offers not only maximal preservation of function but also an excellent possibility for cure, a greater effort should be made to use it as a procedure of choice. This can be done when the patients are very carefully evaluated. The concept of Dr. Churchill and Dr. Klopstock offers satisfactory criteria by which this procedure may be applied.

DR. O. C. BRANTIGAN, Baltimore.—The papers are unanimous in the belief that for patients with pulmonary tuberculosis the use of streptomycin makes all types of surgery much safer. Since the spread or flare-up of disease was most common with pulmonary resections, the beneficial effects of the use of streptomycin in these operations has been most noticeable. Before the use of streptomycin, lobectomy was accompanied by less flare-up or spread of disease and less morbidity and mortality than pneumonectomy. With the use of streptomycin, lobectomy for pulmonary tuberculosis is an extremely safe operation. It should be pointed out that if there is palpable disease in the remaining lobe or lobes perhaps the pneumonectomy is the better operation. Past experience has indicated that before use of streptomycin the patient who survived the pneumonectomy did not later break down with tuberculosis; whereas a high percentage of patients who had lobectomy had recurrence of pulmonary tuberculosis on the operated side, anywhere from six months to two and one-half years after lobectomy. Streptomycin should be considered an acute treatment that will influence the tuberculosis infection but probably will not eliminate the bacteria. Streptomycin, therefore, probably will have no influence on the end result of lobectomy for pulmonary tuberculosis.

DR. CLARENCE CRAFOORD, Stockholm, Sweden.—I should like to tell you that para-aminosalicylic acid, or PAS, is a drug that has been available in Sweden for more than two years for clinical use. It was the work of the Swedish scientist, Jörgen Lehmann, in 1945, which made this drug available. We have used it in series, running it parallel with the use of streptomycin, and we have found that PAS is not as effective as streptomycin in widespread acute lung cases and in cases of miliary tuberculosis and meningitis. We have also had small series in which we have first treated patients with only PAS and then with streptomycin alone, with little effect, but later with a combination of both drugs we have had quite good effect as Dr. Bloch stated. I think PAS is something that should be taken up very seriously for further study. Especially in cases of intestinal tuberculosis we have found this drug to be of great value. Another fact of importance is that the use of PAS does not seem to have any long-lasting toxic effect.

DR. MULVIHILL.—I should like to say a few words in relation to the use of streptomycin in the pleural cavity, as referred to in the experimental work of Dr. Beasley and Dr. Blades and his associates. I had a group of 4 cases, which time did not permit me to report in my paper, in which streptomycin was used in the pleural cavity in tuberculous or tuberculous-mixed-infected empyemas. These were closed spaces without bronchopleural fistulas. The first patient was given 1 Gm. of streptomycin twice a week into the pleural space after evacuation of the thick pleural fluid. The streptomycin was diluted in 100 c.c. of normal saline. The 3 other patients were given the same treatment except that the dosage was reduced to ½ Gm. diluted in 100 c.c. of saline three times a week following evacuation of pus from the pleural space. It was possible to sterilize all these pleural cavities of tubercle bacilli, in varying times. One was sterilized after twenty-two days of treatment, another in ninety days, a third in about seventy days.

The streptomycin levels in the pleural fluid, taken forty-eight to seventy-two hours after the introduction of the drug, varied greatly, from 10 to 160 millimicrograms; it seemed that

the longer the duration of the treatment the greater the concentration in the pleural fluid at a forty-eight hour period after introduction. Simultaneous blood levels ranged from 5 to 10 millimicrograms irrespective of the pleural fluid concentration.

I would also like to refer to another group of 8 cases of old residual empyema spaces following Schede thoracoplasties, with bronchopleural fistulas and pleurocutaneous fistulas. In these a method of treatment with streptomycin was used in which the space was surgically uncovered, and in some cases the lung was decorticated without further mobilization. They were then left widely open. (Slides.) They were treated with a mixture of streptomycin consisting of 1 Gm. of streptomycin and 4 Gm. of dry plasma powder. The open wounds were dusted daily with this mixture, and in all cases healing with clean granulations, such as shown in this slide, was achieved. These patients were not given parenteral streptomycin. In two cases we were able to go ahead from this point and do a secondary closure with immediate healing. This method of treatment has not been previously mentioned. Appreciable blood levels were not obtainable in patients with streptomycin applied to open wounds by this method.

DR. O'BRIEN.—I would like to say one word about Dr. Bloch's discussion. He said that so far as he knew there was no scientific data available to warrant giving smaller doses of streptomycin. It is scientific enough for me to know that it is possible to get exactly the same and possibly better results with smaller doses without having cripples, hopelessly maimed, with nerve involvements, following treatment.

DR. BEATTIE.—I think the suggestion that one reason we found high levels in scarred pleuras was that the vascularity was increased, is a good one. I think it might be expected that streptomycin put into the chest at the time of operation when new tissue spaces are opened and scar is cut across would more likely give high levels than where there is an old scar and streptomycin is put in by thoracentesis. There is one other point that I think might be brought out in the use of streptomycin in the pleural cavity; that is, since the toxic effects seem to be related to the levels of streptomycin that are maintained, it would be well in putting streptomycin in the pleural cavity to be sure to give the streptomycin intrapleurally between times when the intramuscular doses are given parenterally. If a parenteral dose of streptomycin coincides with the intrapleural dose, one can see there would also be high blood levels. We intend to continue some of this work to see what other pathologic effects may be obtained with many repeated intrapleural injections of streptomycin.

DR. MURPHY.--At Oteen we have not had the experience reported by Dr. O'Brien's group in the avoidance of the necessity for surgery by the use of streptomycin. We have used this agent as an adjunct and, as in the other reports this morning have been able to operate on a number of patients by virtue of the use of streptomycin who could not have been prepared for surgery without it. There are so many other factors such as adequate blood replacement, improved pre- and postoperative care, skilled anesthesia, and the Overholt position for resection that it is difficult to place an exact valuation on streptomycin.

All our resections have been done at Oteen in the Overholt position. We did not have the new table, on display here in the lobby, and we do not wish to discourage its sale. As a matter of fact, we have just completed an order for one of these tables. We did, however, have an Albee-Compere orthopedic table and for about ten dollars we were able quickly to modify this table to the Overholt position. (Slides.) The first slide shows the modification of the table with the traction arms reversed. The second slide shows the patient in position ready for surgery.

One further factor of the use of streptomycin needs emphasis and that is that the cooperative study conducted by the Veterans Administration has shown clearly that streptomycin does produce resistance if given over a period of several weeks. This resistance is a factor of the duration of dosage rather than the amount of dosage. For this reason we should be careful and avoid giving streptomycin to patients who do not require it, as in routine thoracoplasty, so that we do not deprive them of its protection if a resection is necessary.

AN ANATOMIC APPROACH TO SEGMENTAL RESECTION

J. GORDON SCANNELL, M.D. (BY INVITATION)
BOSTON, MASS.

TECHNICAL application of the principles of segmental resection has required a precise knowledge of the anatomy of the lung. As individual ligation evolved from mass ligature of the hilar structures, so the more elaborate and unhurried dissection required for segmental resection has developed from the individual ligation technique. Granted that conservation of normal lung tissue is desirable, segmental resection may, under certain circumstances, be the operation of choice. Manifestly, the nature of the pathology involved or merely local technical considerations may preclude that choice. It is not intended here to measure ultimate gain against possible hazard in terms of increased operative time and difficulties with the carefully preserved remnant, but rather to consider segmental resection in terms of the surgical anatomy involved and the growing body of knowledge in that regard.

In 1939, Churchill and Belsey[8] argued that "solely as a concession to operative technics, the lobe has been considered the surgical unit of the lung. The very name of the operation of lobectomy indicates the general acceptance of this concept. A lobe of the lung, however, is in reality made up of a cluster of bronchopulmonary segments." It was recommended that, in bronchiectasis, the segment replace the lobe as the surgical unit.

The concept of the pulmonary segment owes its origin to William Ewart,[10] Victorian physician and pathologist, who, in 1889, ascribed to each lung nine primary "bronchial districts." As Boyden[3] has pointed out, a distinctive feature of Ewart's work was his recognition of the fact that "the lung must be divided into yet smaller regions (than the lobes) in order to attain simplicity in description" and furthermore that these "districts" represented anatomic entities. Ewart's work suffered from a top-heavy mass of detail but remained the only accessible "information concerning the general arrangement of parts within the lung" until 1932. In that year Kramer and Glass[14] rediscovered the primary bronchial districts and applied to them the term "bronchopulmonary segments." Two years later, Nelson,[15] in order to furnish an anatomic basis for postural drainage, described their topography. His description was generally accepted in the English-speaking medical world until, in the past five years, more extensive studies have led to its revision. From the most important of these (Jackson and Huber,[13] Brock,[7] Boyden,[3] Foster-Carter,[11] Appleton,[1] all of which are in virtual agreement as to the disposition of the segments, the simplified schedule shown in Fig. 1 has been drawn up. The need for a generally accepted nomenclature is obvious. At present that of Jackson and Huber, based upon the position of the segment within the lobe, seems to be the most satisfactory.

From the Massachusetts General Hospital and Harvard Medical School.

Read at the Twenty-eighth Annual Meeting of The American Association for Thoracic Surgery, Quebec, Canada, May 31, June 1, 2, 1948.

Although considerable work has been done relative to the bronchial anatomy of the segment, less material has been available concerning its vascular component. So long as thoracic surgery was concerned chiefly with the chest wall and the localization of pulmonary cavities, the need for detailed information concerning the vascular arrangements within the lung was not great. However, as resection of lung tissue underwent its technical development, the need for more precise knowledge became apparent. The stimulus to extend that knowledge from lobe to segment came with the 1939 paper of Churchill and Belsey,

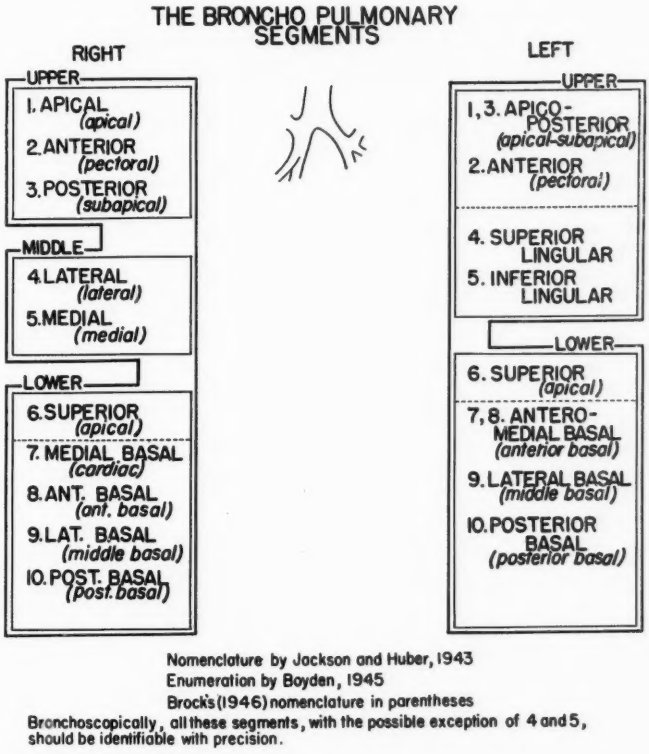

Fig. 1.—Simplified schedule of the bronchopulmonary segments.

previously quoted. At that time the precise anatomy of the lingular bronchus, artery, and vein was described in conjunction with the technique of lingulectomy. Furthermore, the extension of the general principle of segmental resection was advocated and specific suggestions were made relative to the superior and basal segments of the lower lobes on the basis of experience already acquired. In subsequent years, segmental resection of the lingula and of the basal segments considered as a unit have become standard operative procedure, finding particular application in the treatment of bronchiectasis. Other segments than these have also been removed separately where conditions have

warranted, and have been reported from time in the surgical literature.[10, 12] Two such cases—one an anterior segment of left upper lobe, the other a medial basal segment of right lower—have been chosen as clinical examples for the present communication.

These two examples have been selected to call attention to certain anatomic studies in which a method of precise description of intrahilar anatomy has been employed. There are few short cuts to mastery of "segmental anatomy" other than by way of the dissecting room and the operating table, and it is in conjunction with these that the source materials supplied by Boyden can best be appreciated. In an extensive series of dissections[5, 6] this author described and correlated bronchi, arteries, and veins in terms of a prevailing pattern and common variations thereof. It is obvious from studying Boyden's material that few anatomic rules of thumb can be set down concerning the segment but, on the other hand, certain fairly consistent pattern complexes are described that are of considerable practical value in planning resection of a given segment. Predictions as to the resectability of a segment will always be subject to modification by the anatomy and pathology of the local situation found at thoracotomy. However, accurate knowledge of the usual pattern and the common variations is essential to carrying out segmental resection when it is found to be feasible.

In addition to a presentation of the common pattern and variations therein, other aspects of Boyden's work are of surgical importance. He has confirmed the fact that the segment, so far as the pulmonary arterial supply is concerned, is a bronchovascular unit, although at the level of the hilum the pattern of each component must be worked out individually. The pulmonary veins, on the other hand, are intersegmental in nature and more variable than the arteries in their patterns. The bronchial arteries fortunately pose no technical problem at the level of the segment.

Of special interest to the surgeon is the grouping of arteries to the right upper lobe into "recurrent" and "ascending" branches. The former are found in the course of an anterior dissection of the hilum where they are usually deep to the apical and anterior branches of the superior pulmonary vein. The "ascending" arteries to the upper lobe are to be found at the base of the fissure, where they spring from the interlobar portion of the pulmonary artery to supply portions of the posterior and/or anterior segment. Appleton,[2] who introduced the terms "recurrent" and "ascending," has emphasized the variable relationship of the latter to the interlobar division of the posterior vein of the upper lobe.

In the left upper lobe, not infrequently a branch of the lingular artery is found supplying the posterior ramus of the anterior segment (36 per cent of 50 specimens, Boyden[5]). Boyden has considered this to be one of the anatomic hazards of lingulectomy.[4]

To date, Boyden's studies are "complete" only for the upper lobes, while the lower and middle lobes are at present under scrutiny. It seems probable, however, that the upper and middle lobes, together with the medial basal and superior segments of the lower lobes, will prove most amenable to segmental

resection. The disposition of the basal segments makes difficult their differentiation, anatomically, radiologically, and surgically.

CASE 1.—The first of the two clinical examples to be considered was a 35-year-old housewife who, five months prior to admission to the Massachusetts General Hospital, had been ill with lung abscess (Fig. 2). Treatment elsewhere had consisted of bed rest, general supportive therapy, and aerosol and intramuscular penicillin. Symptoms of cough, hemoptysis,

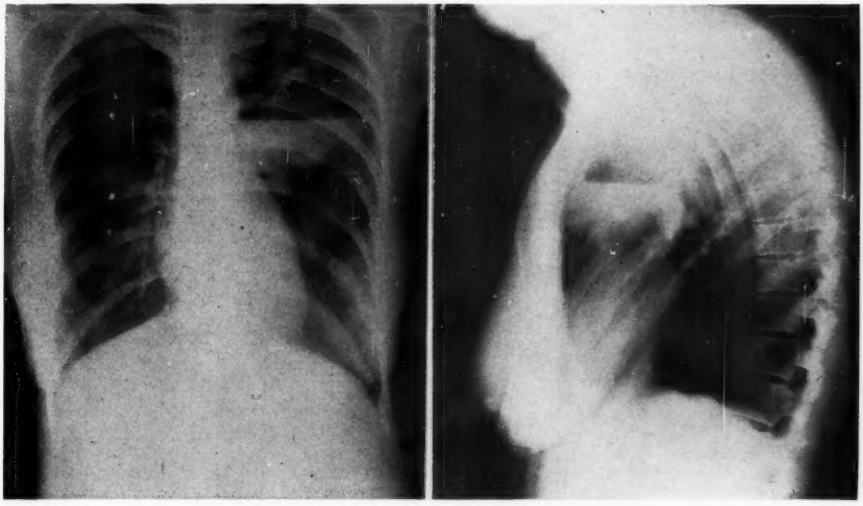

Fig. 2 (Case 1).—Posteroanterior and lateral films taken at the time of the patient's acute symptoms of lung abscess. The anterior segment of the left upper lobe is clearly outlined by disease.

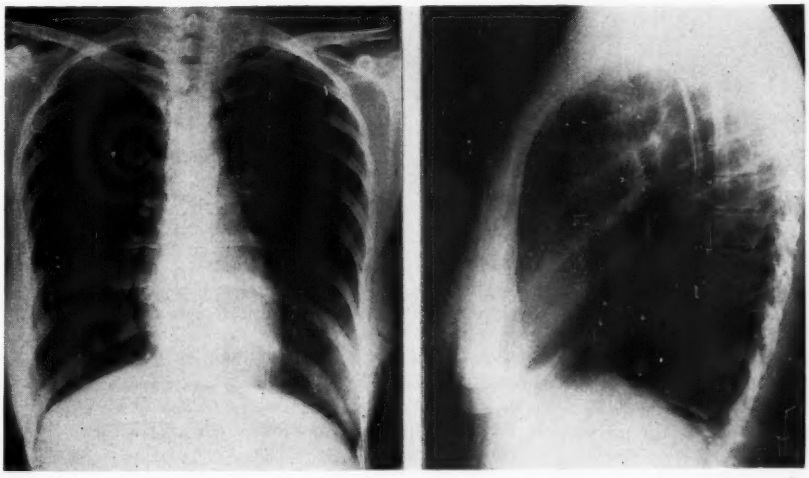

Fig. 3 (Case 1).—Posteroanterior and lateral films that demonstrate the persistent thin-walled cavity localized to anterior segment of left upper lobe.

and fever had subsided, but x-ray examination showed a large, thin-walled cavity to persist in the anterior segment of the left upper lobe (Fig. 3). Operation was advised on the basis that this represented a potential focus of severe, recurrent infection. In view of the localized nature of the disease, a conservative resection was proposed.

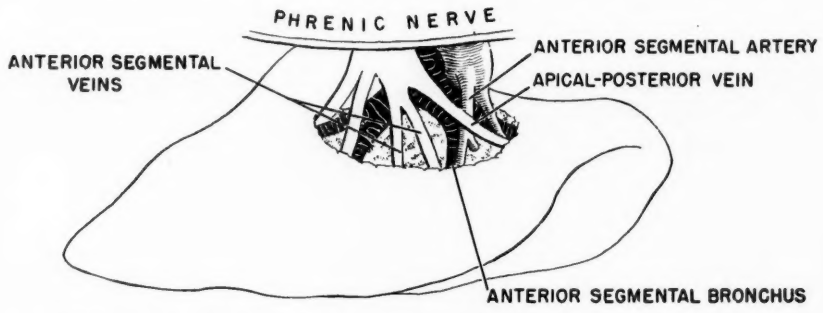

Fig. 4 (Case 1).—The extent of the anterior hilar dissection at the time of operation. Division of the anterior segmental veins afforded access to the lobar bronchus. The anterior segmental artery and bronchus were divided after retraction of the apical-posterior vein.

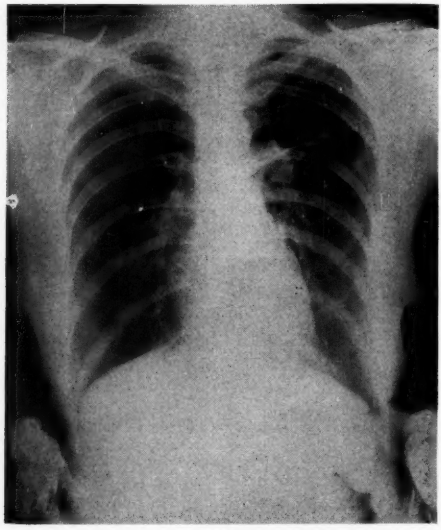

Fig. 5 (Case 1).—One year postoperative. A linear scar is apparent at the site of resection of the anterior segment of left upper lobe.

At the time of thoracotomy, adequate exposure was obtained by resection of the sixth rib. The pleural space was observed to be free of adhesions except over the anterior segment of the left upper lobe, and these were readily divided by sharp dissection. The remainder of the left upper lobe appeared essentially normal. The oblique fissure was anatomically complete.

Dissection of the hilum at the base of the fissure demonstrated the lingular artery, which, in this instance, furnished a small branch to the posterior aspect of the anterior segment. The arch of the pulmonary artery was followed upward over the left upper lobe

bronchus and arterial branches to apical-posterior and anterior segments accurately identified (Fig. 4). All the subdivisions of the superior pulmonary vein, lying on the anterior aspect of the hilum, were exposed and the apical-posterior vein was retracted upward to afford access to the anterior segmental artery. The anterior segmental branches of the vein were divided, one large lymph node dissected out of the crotch of the upper lobe bronchus, and the superior division of this bronchus exposed. After division of the anterior segmental artery, the superior bronchial division could be followed outward to its bifurcation into anterior and apical-posterior branches. The anterior branch was gently occluded and, by inflation of the lung, demonstrated to supply the area of disease. It was therefore divided, closed with interrupted fine silk sutures, and, after incision of the pleura along the line demarcated by inflation, the segment removed from below upward without clamps.[16] A few hemostatic and aerostatic sutures of fine silk were necessary. The wedge-shaped defect in the lobe was closed by approximating the upper surface of the lingula to the apicoposterior segment, a maneuver that covered the bronchial stump with normal lung.

Postoperatively the patient expanded the left upper and left lower lobes well, both clinically and by x-ray. The latter revealed a circumscribed area of density in the region of the resection which was interpreted as probably hematoma, possibly infarction. One year later this was demonstrated as a linear scar (Fig. 5). Clinically, the patient is well.

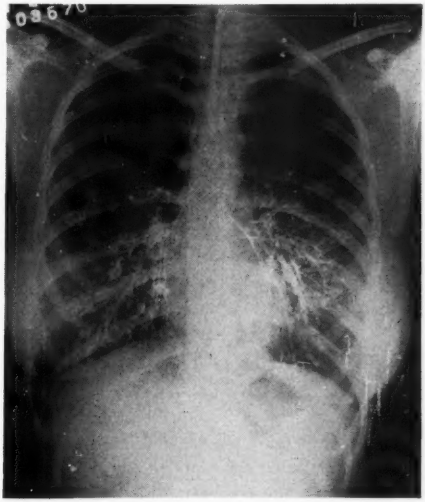

Fig. 6 (Case 2).—Posteroanterior bronchogram demonstrating bronchiectasis in medial segment of right middle lobe, medial basal segment of right lower, and inferior lingular segment of left upper lobe. This localization was confirmed by a right lateral view and right and left oblique views not shown.

Case 2.—The second example was that of a 14-year-old schoolgirl with bilateral bronchiectasis. Since the age of 3 years the patient had been prey to frequent bouts of upper respiratory infection, which had become almost continuous. She raised, on the average, one-half to one "cup" of yellowish, tenacious sputum daily. She had managed to keep up at school, but bore many of the psychologic stigmas of the disease.

Plain films showed bilateral disease in both lower lung fields. A bronchogram demonstrated bronchiectasis in the medial segment of the right middle lobe, the medial basal segment of the right lower lobe, and inferior lingula segment of the left upper lobe. No disease could be demonstrated in the basal segments of the left lower lobe.

Prior to operation, bronchoscopy was carried out. A normal right upper lobe orifice was inspected through a right-angle lens and a trifurcation visualized. The mucosa about

the middle lobe orifice was somewhat thickened and considerable mucopurulent sputum could be seen coming from it. The orifices of the superior segment and basal segments of the right lower lobe were normal except the medial basal orifice, from which considerable pus exuded. The left bronchial tree was examined and no abnormalities were noted.

After suitable preparation, a right thoracotomy was performed. Resection of the sixth rib gave excellent exposure. The pleural cavity was essentially free of adhesions except at the anterior tip of the middle lobe. The fissures were well developed except for anatomic fusion of the anterior half of the minor fissure. A middle lobectomy was carried out. The line of demarcation between middle and upper lobe was demonstrated by inflation, and the lobes were divided by stripping from below upward. A small apron of pleura was fashioned from the middle lobe to cover the resultant raw area in which there was no significant bleeding or air leak.

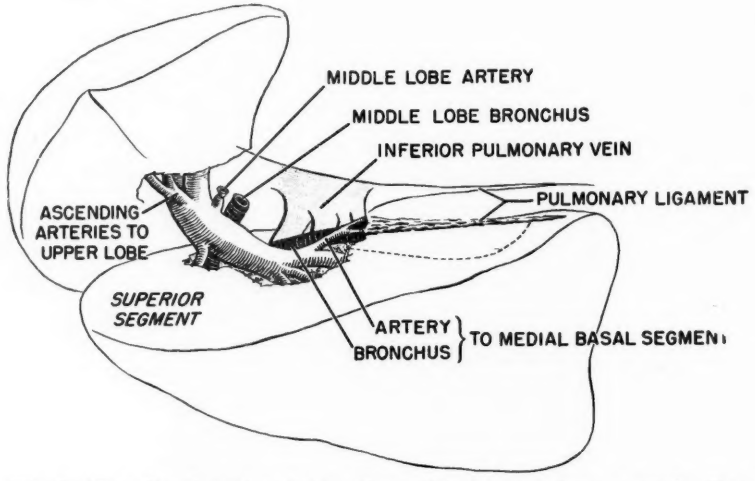

Fig. 7 (Case 2).—Operative sketch. The middle lobe has been removed. The relationship of the artery, bronchus, and veins to medial basal segment of right lower lobe is shown. The surface area of that segment and its relationship to pulmonary ligament are indicated by a broken line.

Attention was then directed to the lower lobe which appeared entirely normal except for a collapsed, inelastic medial basal segment, which lay just anterior to and beneath the pulmonary ligament. The dissection was started along the pulmonary artery and the large anterior basal branch to the lower lobe demonstrated (Fig. 7). Springing from its medial aspect was a sizable branch that supplied the medial basal segment. This was divided. The pulmonary ligament was divided up to the inferior pulmonary vein. This lay in the plane between medial and posterior basal segments, and no surface tributaries from the medial basal segment were observed. The anterior surface of the vein was exposed and a few branches crossing this plane were divided and ligated. The medial basal bronchus was then readily exposed as it emerged from beneath the pulmonary artery. The bronchus was divided, closed with interrupted silk, and the segment readily stripped from the remaining basal segments of the lower lobe. There was relatively little bleeding and no air leak. The resulting defect tended to fold over on itself and few sutures were required. The bronchus lay covered within the substance of the lung.

The patient's postoperative course was satisfactory, with excellent expansion of both upper and lower lobes.

In the two cases selected, the indications for segmental resection seemed clear, and the local situation, particularly with regard to the completeness of

the fissures and lack of acute inflammation, favorable. In both, the anatomic patterns were straightforward.

In the first case, the anterior origin of the arteries was as expected. According to Boyden and Hartmann, the artery to the anterior and lateral portions of the anterior segment arises consistently from the pars anterior of the left pulmonary artery. In about one-third of specimens, as here, the apical artery also has an anterior origin. The branching of the superior pulmonary vein is worthy of comment, first in regard to the anterior and relatively superficial position of its branches, and second, in regard to the presence of two branches to the anterior segment.

In the second case, the accessibility of the pulmonary artery as it lay on the anterior aspect of the right lower lobe was striking. The relation of the medial basal segment to the pulmonary ligament was in accord with Brock's description of the "cardiac" segment. It is this segment that forms a separate "cardiac" lobe in most quadrupeds, and in man is not infrequently marked by an incisure (24 per cent).* In the case described, its relation to the inferior pulmonary vein was the key to the situation.

SUMMARY

1. The significance of the bronchopulmonary segment has been reviewed with reference to segmental resection of the lung.

2. Recent studies of bronchovascular anatomy have been discussed.

3. Segmental resection of the anterior segment of the left upper lobe and medial basal segment of the right lower lobe have been presented with illustrative cases of each. Emphasis has been laid on the problems of surgical anatomy involved.

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*Reported by Dr. Franklin Smith at a meeting of the American Association of Anatomists, 1948.

DISCUSSION

DR. ROBERT KLOPSTOCK, Jamaica, N. Y.—I have been fortunate and privileged to be associated with Dr. Churchill from 1939 to 1942, and to carry on studies under his guidance and stimulation, on the surgical pathology of the lung. These studies revealed, among others, that the distribution of the chronic surgical diseases of the lung—including chronic tuberculosis—has corresponded with the bronchovascular segment of the lung.

The localization and the radiographic analysis of pathologic processes in the chest could be improved greatly by using body-section radiography in the anteroposterior view. But even this method fails to demonstrate clearly the segmental and lobar distribution of the pathology present because it does not resolve the overlapping of the bronchovascular segments as visualized in the anteroposterior plane, for the branching of the bronchovascular structures takes place, rather, in the sagittal plane. Therefore, the lateral body-section radiography was devised by Mr. J. L. Mathias and myself in 1943, and has been used since at the Triboro Hospital, Jamaica, N. Y. Each patient considered for any type of surgery for disease of the lung was hence tomographed both in the anteroposterior *and* in the lateral view. This method was found most satisfactory to reveal pathologic conditions of the chest and of the lung in particular, with a clarity not previously achieved, as follows: (1) Hidden hilar and parahilar pathology. (2) The lobar and segmental distribution of chronic pulmonary disease with particular attention to the apex of the lower lobe, the middle lobe, the lingula: (a) in cases of tuberculosis *the* information necessary if lobectomy has to be considered vs. thoracoplasty or (b) in most carefully selected cases if lobectomy with resection of adjacent diseased segment has to be considered, or (c) if resection of a diseased individual segment alone is considered, (d) in cases of bronchiectasis both obviating bronchography in many instances and delineating the involved segments to be resected individually. (3) The relation of the site of the disease to the fissures, also with particular attention in cases of pulmonary tuberculosis if lobectomy has to be considered. (4) The demarcation of the relative volume of lobes involved and uninvolved by disease with particular attention to the pathophysiologic considerations. (5) The differentiation of a given intrathoracic pathology as to its localization in- or outside of pulmonary parenchyma. (6) Possibilities in the study of coaretation of the aorta, patent ductus arteriosus, arteriovenous fistulas of the lung, aneurysma of the great vessels.

Having this information of a more correctly interpreted pathology, a planned outline of the respective surgical procedure can be drawn. (Slides.)

DR. RICHARD H. OVERHOLT, Boston.—I am sure a great many future patients suffering from bilateral pulmonary disease will appreciate the help they will receive because of the surgeon's ability to remove segments. They will unconsciously thank such pioneers as Drs. Churchill, Belsey, Boyden, Blades, Nelson, and Scannell, who has again brought this important concept of treatment to our attention.

When we first became interested in segmental resection, it was applied only in patients suffering from bilateral disease, for in them any loss of functioning pulmonary tissue might compromise a satisfactory result. However, as time went on, with greater knowledge of the anatomy of the various segments and improved technique in developing the intersegmental plane, which resulted in fewer complications, it has been possible to utilize individual segments as the unit of excision in certain cases of unilateral bronchiectasis and in other conditions as well.

(Slides.) I should like to relate circumstances in one case which will illustrate why it is important to limit the resection to segments when possible in unilateral disease. Recently this patient presented himself with a giant cyst in the right lung which had caused almost a total collapse of that lung. Upon exploration, it was found that the cyst represented a check valve mechanism in one of the subsegments of the upper lobe. The resection was therefore limited to that subsegment and you will see (slide) the appearance both before and after the removal of the subsegment which contained the cyst. In the next film (slide) you will see a routine follow-up x-ray view which was taken when the patient reported to his doctor six

months later. At this time an abnormal shadow was found in the left upper lobe which turned out to be a primary carcinoma. If we had originally used a lobe for the unit of excision in the treatment of the cyst on the right, we would have closed the door to treatment of the carcinoma which subsequently developed in the left lung.

Gradually the principle of segmental excision has been extended to include almost every one of the eighteen segments. It has been possible to remove them individually or in groups. In this slide are illustrated various segments which have been removed and the condition for which the operation was performed—bronchiectasis, tuberculoma, solitary tuberculous cavity, metastatic tumor, abscess, cyst, and benign tumor.

It is timely to project a thought about segmental resection in tuberculosis. Not infrequently the superior segment of the lower lobe is found to be involved when exploration is done for upper lobe disease. In that event it is preferable to include that segement in the resection with upper lobectomy rather than abandon resection or resort to pneumonectomy. We have also had occasion to do a more limited resection than previously planned. A superior or posterior segment may contain all the gross tuberculosis disease and a segmental resection may suffice. It is too early to comment on end results. In tuberculous subjects the resection has been limited to segments in nine cases. From this early experience it would seem that, in the future, segmental resection will have a definite place.

DR. F. A. HUGHES, Memphis.—I have been interested in segmental resection and also a combination of streptomycin and resection, and I believe it stands a good chance of greatly improving the treatment of certain cases of tuberculosis. Recently, we have done three segmental resections for tuberculosis. We find in some cases it is preferable not to do the usual initial hilar dissection of the segment, but to start the dissection of the pathology peripherally. In contrast to bronchiectasis, it is usually possible to demonstrate at the operating table the extent of the lesion. Recently we resected the posterior-apical and anterior segment of the upper lobe and the superior segment of the lower lobe. The cavity in the superior segment was draped over the artery to the basal segments. The patient surprisingly had an airtight remnant after the operation and has made an uneventful recovery to date. Apparently selective resection, with the protection of streptomycin, will hasten recovery without the necessity for as extensive or as radical a thoracoplasty.

DR. OSLER ABBOTT, Atlanta, Ga.—I want to mention one thing which has been under discussion in segmental resection, that is, closure of the defect on the left. When we were first presented with this method, considerable discussion arose in regard to the method of closure. If a cleft were left so that there was a tendency for the lung to close without distortion, that should be done. Others feel that it restricted pulmonary activity. I have been disappointed with fibrin foam or any coagulating material in the cavity, because of an occasional instance of clotting hemothorax. I was very much opposed to leaving a raw area, and have done subsequent series with and without closure of the raw area. I think with the surface exposed great attention should be paid to pulmonary function, and it seems to be improved when no attempts are made at closure. Also, other remaining segments should be sutured to the remaining intact lobe, above in order to prevent rotation of the preserved segment with associated obstruction to the segmental bronchus.

DR. ARTHUR S. W. TOUROFF, New York.—The presentation that we have just heard sets forth in detail a method which permits us to correct not only a number of conditions that occur spontaneously, but also several that follow operation. I was particularly interested in Dr. Scannell's paper from the viewpoint of correcting some of the poor results which we have had following surgical treatment of abscess of the lung. Prior to World War II, Dr. Neuhof and I published a series of papers concerning the afore-mentioned subject and it was our impression, based upon the follow-up observations that we had made up to that time, that early operation in cases of acute putrid pulmonary abscess was almost invariably followed by prompt and permanent cure. Recently, I reviewed all of our material and found that we had operated upon 154 patients with acute putrid abscess of the lung prior to Jan. 1, 1943. There were 4 operative deaths and 150 surviving patients. Forty-two of the

latter could not be followed for the minimum period of five years, which was set as the basis of the study, and therefore were eliminated from further consideration. This left 108 patients who could be followed for at least five years. Of the 108 cases, 93 are well. However, much to our surprise, there were 15 patients who were left with residual postoperative pulmonary cavities or bronchiectasis. It came as a distinct shock to me to learn that 15 of 108 surviving patients were not cured. While not all of the 15 patients presented symptoms, they all had demonstrable, localized structural changes in the lung. Accordingly, I would like to retract the statement which I made prior to the War, to the effect that early operation in cases of acute putrid pulmonary abscess almost invariably is followed by complete and permanent cure. This was an error which was due to the fact that our period of follow-up observation was too short. Dr. Scannell has emphasized the value of segmental resection, and I think that the latter offers us a simple method of correcting some of the poor results that we have had following the surgical treatment of certain types of pulmonary infection.

A TECHNIQUE FOR PULMONARY SEGMENTAL DELINEATION

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PHILADELPHIA, PA.

PULMONARY surgery has made rapid and steady progress from the earlier days of large mass ligature of hilar structures to this day of careful segmental delineation and resection. A clearer understanding of the anatomic relationships of lung structures, more refined surgical technique, and better anesthesia have all aided in this progressive trend.

Bronchopulmonary segments of the lungs are clear-cut entities, well described and recognized. The widely adopted nomenclature of Jackson and Huber[1] is becoming more familiar and clearly defines these segments (see Fig. 1). The segments have their independent hilar bronchovascular structures which resemble the main hilar structures of the lung. Thus, the left lung has two main lobes, the upper and lower. These are further subdivided. The upper lobe bears the following segments; an apicoposterior, an anterior, and the lingula—the homologue of the middle lobe (which is further divided into an inferior and superior division). The lower lobe gives off a superior segment, and four basal segments; anterior, posterior, medial, and lateral. Similarly segmented is the right lung, which has an upper lobe, middle, and lower lobe. The upper lobe is divided into three segments: the apical, anterior, and posterior. The middle lobe is divided into lateral and medial segments, while the lower lobe gives off a superior segment and the basal segments—anterior, medial, lateral, and posterior.

Pathologically, these segments may be a localized seat of infection. Bronchiectasis very commonly is confined to segmental distribution. Pulmonary abscess, cystic disease, and tuberculosis may be located essentially within a bronchopulmonary segment. Pulmonary disease is frequently bilateral and since we are primarily interested in effecting a cure with minimal sacrifice of good functional lung tissue, a careful study to localize the disease processes within pulmonary segments is of prime importance. Bronchiectasis, for example, which is so commonly a segmental disease with bilateral distribution, should be studied by careful bronchography. It will be found that the most frequently infected segments are: (1) on the left, the lingula and the basal segments of the lower lobe; (2) on the right, the middle lobe and the basal segments of the lower lobe. Thus, the superior divisions of the lower lobe bronchi can often be saved, which is a sizable area of good functioning lung tissue. Similarly, it is often found that only a portion of the basal segments shows pathologic change, and again, it is important to save as much good lung tissue as possible and to remove only the areas of pathology.

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Until recently the techniques for resection of isolated pulmonary pathology have been very crude. They have consisted for the most part of a "clamp-cut" method across pulmonary tissue, only presumed to be anatomic. This technique is associated with many disadvantages. In the first place, often, either too much or too little lung tissue is removed. Furthermore, it is unnecessarily traumatic, and excess tissue is destroyed by the crushing of clamps and the suturing of bleeding points. Finally, it is not anatomic.

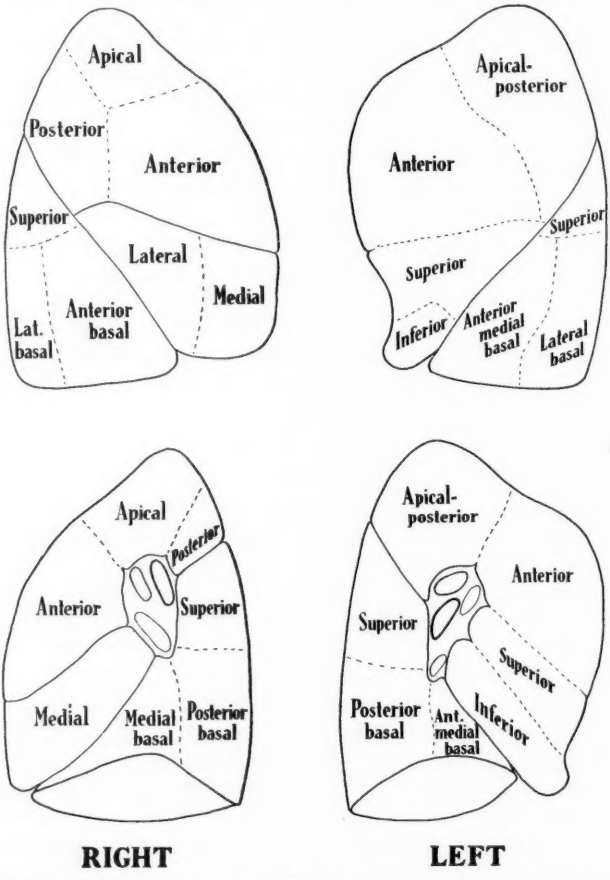

Fig. 1.—The bronchopulmonary segments. (From Jackson, C. L., and Huber, J. F.: Dis. of Chest 9: 322, 1948.

More recently, the anatomic approach has been used. Churchill and Belsey, and Overholt and Langer[2] have recently described their excellent techniques for segmental resection, utilizing the traction-dissection and differential inflation methods. Others, including Clagett and Deterling,[3] have adopted the anatomic approach.

The technique we employ closely resembles that of Overholt's up to a certain point. Exact identification and severance of the bronchus, arteries, and veins belonging to a specific segment permit subsequent surgical removal of the segment. For example, if the disease process involves the basal segments of the left lower lobe, the common basal bronchus is identified as a continuation of the left main bronchus after the superior division bronchus has been given off. This is divided and a metal suction tip is introduced into the proximal cut bronchus and directed toward the accessible bronchi, aspirating the secretions from the tracheobronchial tree. The proximal stump is closed with interrupted end sutures of No. 35 stainless steel wire on swedged needles. A clamp is kept on the distal bronchial stump. The segmental artery to the basal divisions is identified. It is merely the distal continuation of the left main pulmonary artery after the superior division branch and the lingular branch have divided. The artery is doubly ligated with No. 40 cotton. The veins from the basal segment, usually three or four in number, can be traced to the inferior pulmonary vein, at which point they are divided and ligated with No. 40 cotton. Up to this point our technique is similar to the usually described methods. In our experience the line of cleavage between segments has not always been clear cut. Whereas in some cases this cleavage can be accurately established, it is in the less diseased segments that accurate demarcation is often impossible to ascertain. The method usually employed in such cases is to inflate the lung differentially. That is, the bronchus to the diseased segments is occluded or severed and the remaining portion of the lung is inflated by positive pressure exerted on the gas machine bag. The occluded segment is expected to remain airless, but what is commonly seen is that a sharp line of differentiation between aereated lung and the occluded segment does not exist. Air does cross these intersegmental fissures, apparently by means of small air passages (Kohn's pores), and as a result, even the segment which has been occluded may become partially or completely inflated with air. One is then faced with a real problem as to how to establish the visceral intersegmental cleavage plane.

Clagett and Deterling have described the technique of stripping the bronchus and vessels with traction dissection and thus bluntly establishing a plane of cleavage. This plane of cleavage is an area which gives the least resistance to blunt dissection. Again, while this technique can often be employed, it is not infrequently seen that when removing segments, especially the smaller ones, portions of adjacent segments are torn off, or, smaller bronchi of the same segment are torn leaving portions of that diseased segment attached to the remaining lung. In this situation more bleeding is encountered.

Recognizing the occasional difficulty met in attempting to establish a clear-cut line of delineation between segments, we have employed a simple method of distending and staining the diseased segment so that it stands out clearly from the other segments. This method, while not routinely employed in our segmental dissections, is, however, found to be valuable when a clear line of cleavage is not discernible.

TECHNIQUE

Methylene blue as the coloring stain is mixed with hydrogen peroxide. A few drops of methylene blue are added to 15 c.c. of hydrogen peroxide. The resulting solution is then slowly injected into the distal (cut) bronchus of the segment to be resected. No pressure is necessary to force this solution to reach the ramifications of the segment. The action of the hydrogen peroxide, when it is in contact with the tissues, is to liberate oxygen, which then bubbles and fizzes and pushes the colored solution throughout the segment. This results in a blue-stained segment which is turgidly distended by the large amount of oxygen liberated within its tissues (Figs. 2 and 3). This segment then stands out clearly and unmistakably from the adjacent normal lung tissue. The line of delineation between the segments is well established. Since the bronchus and vessels of the segment have already been divided, the segment can now be dissected with relative ease. Furthermore, if there is any doubt about the exact vessels which supply the segment, division of these can be deferred until the staining-distention exposes their distribution.

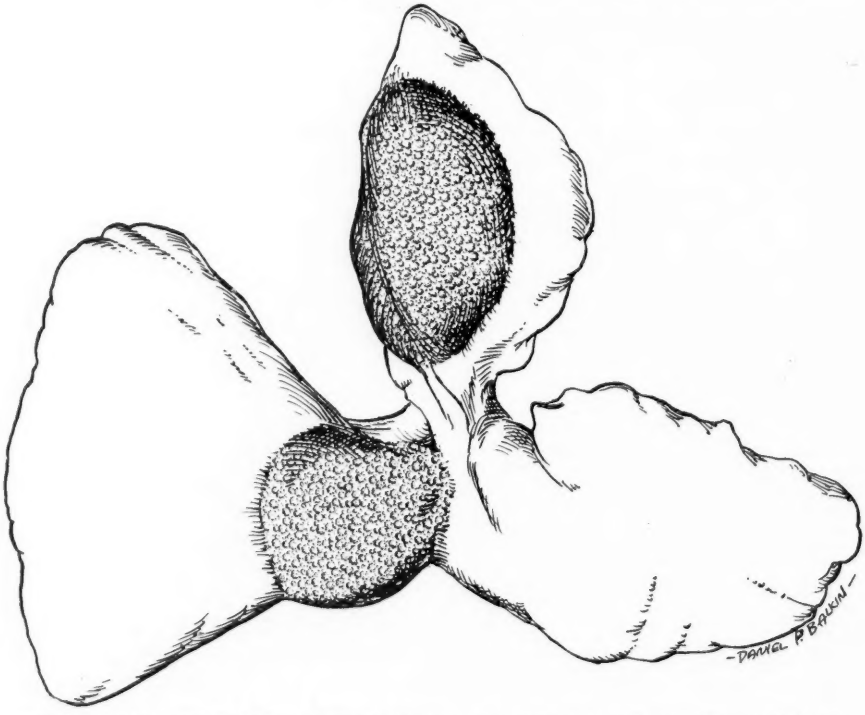

Fig. 2.—Shaded area indicates segments of dog lung distended with peroxide (H_2O_2) and methylene blue.

Details of Technique.—

1. It is preferable not to crush the distal bronchus with a clamp, but rather to occlude it gently.

2. A special adaptor has been used, devised by Dr. Louis R. Davidson, of New York, which fits tightly into the lumen of the bronchus and is equipped with a stopcock. This, furthermore, fits into a Luer Lok syringe so that no spillage occurs.

3. Excess pressure should be avoided when injecting the solution because this will cause soiling of the surrounding tissues by spilling over.

4. When removing the adaptor, a clamp should be laid ready in place over the bronchus for immediate closure to avoid regurgitation.

5. Wet sponges should be placed to wall-off surrounding tissues in the event that spillage might occur.

6. To separate the segment, blunt and sharp dissectors are usually employed. Much of the dissection is blunt (finger dissection). Very little bleeding and very little air leakage results when the proper cleavage is developed. The raw surface of lung remaining is covered with a warm moist sponge for a few minutes. It is surprising to note that this surface is relatively dry and has a minimal amount of air leak.

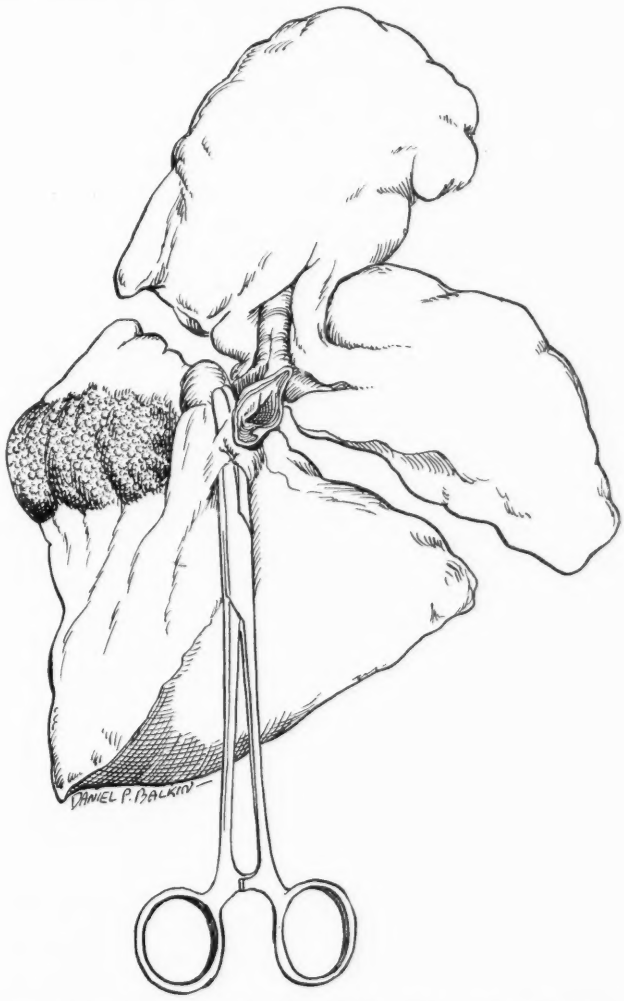

Fig. 3.—Segment of dog lung distended with peroxide (H_2O_2) and methylene blue. Clamp occludes segmental bronchus.

The stump of the bronchus is now covered with adjacent pleural reflection or a free fascial graft. A rubber catheter, No. 24, is placed intercostally for drainage and continuous suction and 15 cm. of water are used for forty-eight hours to re-expand the remaining lung tissue.

Postoperatively, endotracheal aspirations are repeated as often as every hour when necessary in order to keep the tracheobronchial tree clear. Patients are ambulated at the first or second day postoperatively, which aids coughing and deep breathing. The progress of the patient is carefully observed by regular x-ray views and fluoroscopy of the chest. In an uneventful case the patient will usually feel quite well by the third or fourth day and will be ready for discharge from the hospital by the seventh to tenth day.

The complications occasionally seen are (1) atelectasis, lack of re-expansion of remaining lung tissue which can be treated by repeated bronchoscopy and insistence upon coughing; (2) fluid in the pleural space, which should be aspirated when there is a significant amount; (3) empyema, an uncommon complication, since good bronchial closure and chemotherapeutic agents usually circumvent this; (4) bronchopleural fistula, usually the result of inadequate bronchial closure, early complete re-expansion will help to eliminate this.

ANALYSIS OF CLINICAL DATA

During the year of 1947 it was found necessary to utilize the methylene blue injection method in a total of ten cases because of extreme difficulty in identifying the intersegmental cleavage plane. Nine of these cases represented segmental distribution of bronchiectasis. One patient had a giant tuberculous cavity in the left upper lobe. In all cases it was possible to accomplish the desired segmental resection, thus obviating the necessity of lobar resection. The distribution of disease in these cases was as follows: (1) Lingula, and anterior segment of left upper lobe, two cases; (2) lingula, and both anterior-medial basal and lateral basal of left lower lobe, one case; (3) lingula, and superior segment of left lower lobe, one case; (4) apical-posterior, and anterior-medial basal of left lower lobe, one case; (5) lingula alone, two cases; (6) lateral basal of left lower lobe and lateral basal and posterior basal of right lower lobe, one case; (7) superior segment of right lower lobe, two cases. Eight of these cases were uncomplicated postoperatively. Two of the patients developed empyemas which were local in character and associated with bronchopleural fistulas. Open thoracotomy and drainage of the localized empyema spaces resulted in cure in both of these complications. These two complications probably could have been avoided by a more vigorous attempt to re-expand the remaining lung tissue so as to obliterate all of the pleural space early and completely.

CONCLUSIONS

1. Segmental pulmonary resection is a surgical technique of considerable value. It is indicated in many instances and is quite feasible. Maximal good lung tissue is spared in the removal of the pathologic segments, and it is especially valuable where bilateral resection is contemplated.

2. A new technique for more adequately establishing intersegmental cleavage planes is described.

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ENDOBRONCHIAL OCCLUSION DURING PULMONARY RESECTION

Preliminary Report

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INTEREST was aroused in the problem of controlling bronchial secretions at Duke Hospital during an analysis of 125 cases of pulmonary resection performed from 1937 to 1947; it was observed that ipsilateral and contralateral spreads had occurred in twenty-seven cases, or 21.6 per cent. In this group there were five deaths, all directly attributable to the spread. A survey of the literature revealed that our figures were not in disagreement with those of other clinics, and our methods of control of bronchial secretions were the same as those in general use.

These methods of control fall into three general categories. The first group includes preparatory measures, such as chemotherapy, postural drainage, and the postponement of operative procedures to the summer months when upper respiratory infections are at a minimum. The second group points at active control of secretions during the removal of the infected lung segment, namely, tracheobronchial aspiration by catheter, mechanical blocking of the bronchi, and positioning of the patient with dependence on gravity drainage. The third group is preventive as well as therapeutic and includes chemotherapy, deep breathing exercises, bronchoscopy, and enforced coughing.

Inasmuch as no one method will be completely successful in this problem, it is obvious that the preoperative preparatory measures of chemotherapy and enforced postural drainage must always be used, and the postoperative preventive measures should be employed routinely. Although tracheobronchial aspiration by catheter has been one of the most commonly used methods in the second group, it is not entirely satisfactory, as evidenced by our own percentage of spreads. The positioning of the patient during operation with dependence on gravity drainage of the secretions, particularly as advocated by Overholt,[1] has gone far in reducing the danger of spreads, but has not completely eradicated it.

There have been many instruments designed for mechanically blocking the various bronchi with the subsequent isolation of one or more lobes, such as the endotracheal airway described by Gale and Waters in 1931 (Fig. 1), the combined tracheoscope and anesthetic tube devised by Magill in 1936 (Fig. 2), the technique of bronchial tamponade advanced by Crafoord and described by Nosworthy in 1941 (Fig. 3), and the bronchial occluder reported by Halton in 1943 (Fig. 4). All have been described in more detail in a previous report.[2]

Since none of these instruments, in our experience, could be depended upon to perform the job for which it was designed, it was felt that an endobronchial

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balloon could be devised to obstruct the portion of lung to be removed, and to provide aspiration of air and secretions from this obstructed segment. The most obvious criticism of any instrument constructed around a balloon has been its lack of dependability, a tendency to slip out of place at inopportune times. This has been circumvented by the use of a metal holding apparatus, which fits around the balloon, and which maintains its position through the protrusion of

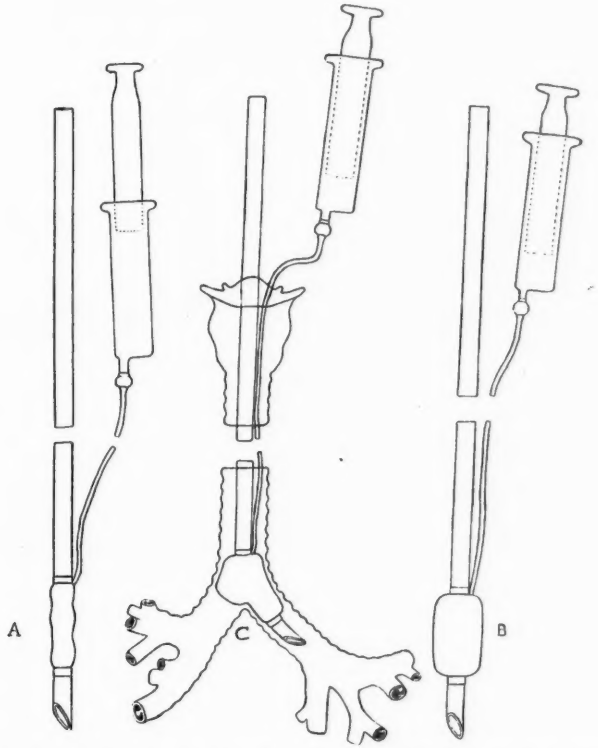

Fig. 1.—Gale and Waters endotracheal balloon with obstruction of the main bronchus at the carina.

numerous small points (Fig. 5). The instrument was first used in pulmonary resections in dogs, and it was shown that (1) no harmful effects were produced, (2) complete occlusion of the bronchus was obtained, (3) dislodgment during operation was very unlikely, (4) there was a wide margin of safety, and, (5) there was very little interference with anesthesia.[2] It was subsequently used in resections in patients, and a report was made of the results and complications during the first year.[3] Since the results appeared fairly satisfactory, the instrument has been used for another year, and the indications, effectiveness, and complications of its use are embodied in the present report.

INDICATIONS

Use of this instrument is indicated in any resection for suppurative pulmonary disease, including bronchiectasis, lung abscess, carcinoma with secondary suppuration, and tuberculosis. In its present form, it is not applicable in upper lobectomies; it is hoped that a modification of the instrument will soon be available for this particular operation. The presence of bilateral disease, particularly bronchiectasis, does not constitute a contraindication. There is ample room for suction through the endotracheal tube. On the contrary, blocking the most seriously diseased portion relieves the anesthetist of much more purulent material spilling out into the major bronchi. The balloon is particularly indicated in patients with decreased pulmonary reserve. Positive pressure anesthesia plus constant inflation of the upper lobe in cases of lower lobectomies may be maintained throughout the procedure without the hindrance to the surgeon caused

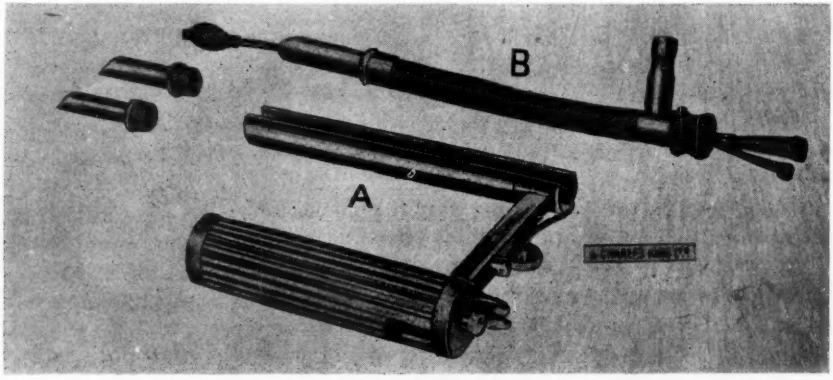

Fig. 2.—Magill's combined tracheoscope and anesthetic tube.

by the inflation of the lobe being resected. The presence of atelectasis in the affected lobe is a definite aid to the surgeon, not only in allowing more operating space, but also in the delineation of the interlobar fissure. Although we have not as yet used the instrument in a segmental lobectomy, since the child's size is not yet available, use of this same principle in differentiation of the segments should certainly be an added advantage. In cases of tuberculosis, the presence of large amounts of hyperplastic tissue at the contemplated site of placement of the balloon constitutes a definite contraindication to the use of the instrument. This is discussed under complications further on in the report.

TECHNIQUE

During the past year very few changes have been made in the actual construction of the instrument. The carrier tube has been shortened so that the site of placement of the balloon is as close as possible to the tip of the bronchoscope. The instrument table has been discarded and the manometer and suction bottle incorporated in a metal case, thus providing a small compact unit at the operating table.

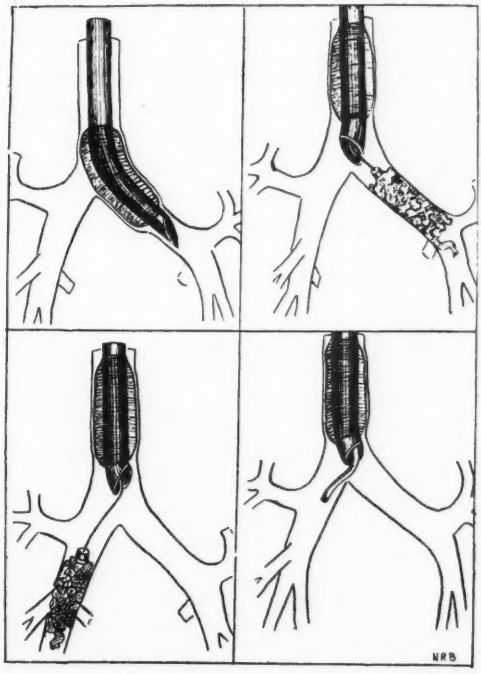

Fig. 3.—Crafoord's technique of bronchial tamponade.

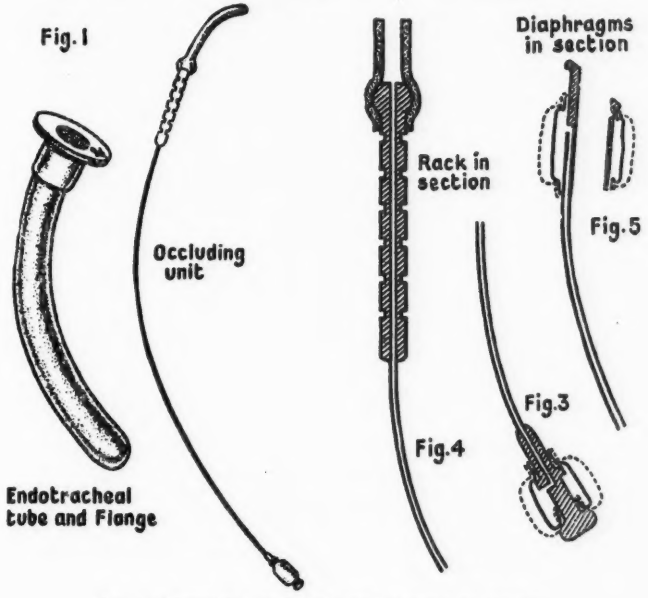

Fig. 4.—Bronchial occluding unit devised by Halton.

There have been no changes in the technique of using the instrument, save for variations in anesthesia. In approximately one-half of the cases intravenous pentothal and topical anesthesia have been used for bronchoscopy and induction; in the others, the pentothal has been used after bronchoscopy and placement of the balloon are completed. The use of pentothal for induction of general anesthesia has definitely improved the entire procedure. At the present time an average of twenty minutes is required from the beginning of topical anesthesia to the completion of placement of the balloon and beginning of general anesthesia.

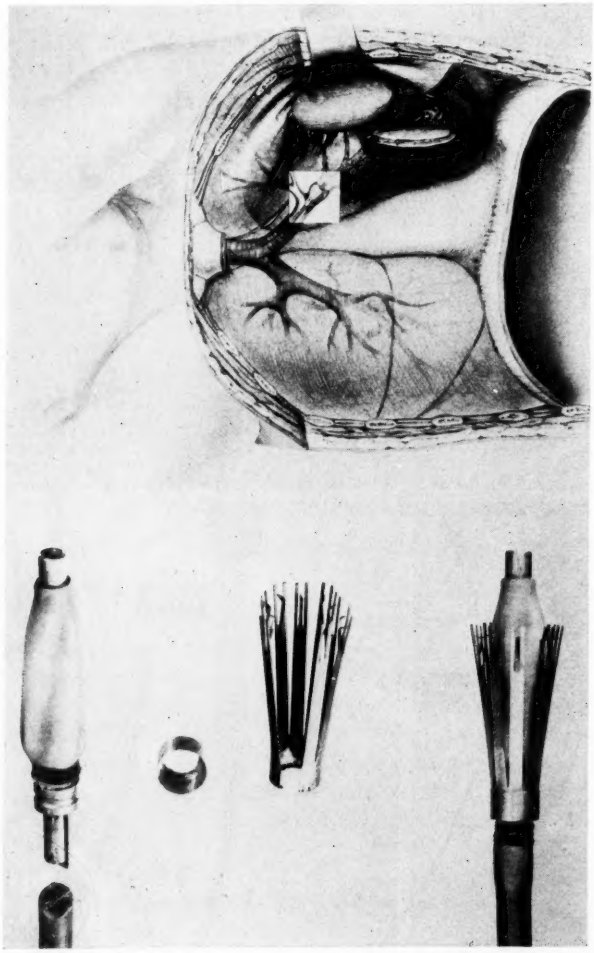

Fig. 5.—Endobronchial balloon (author's) and its diagrammatic use in a left lower lobectomy.

RESULTS

During the past twenty-four months this instrument has been used in the forty-four cases as shown in Table I.

TABLE I.

DIAGNOSIS	LOBECTOMY	PNEUMONECTOMY	EXPLORATORY THORACOTOMY	DRAINAGE
Bronchiectasis	15	1		
Abscess	4	2		
Bronchiogenic carcinoma		1	4	
Tuberculosis	1	14		
Foreign body	1			
Empyema				1
Totals	21	18	4	1

The empyema case was incorrectly diagnosed preoperatively as a lung abscess.

There were six deaths in this series of cases. Three of these patients died the day of operation and immediate autopsy in two revealed no evidence of spread. Autopsy was refused in the third case; death occurred very shortly after removal of the balloon and during hilar manipulation. Bronchoscopy at the time of death revealed the bronchi on the unaffected side to be free of secretions. The other three deaths occurred at sixteen, twenty-three, and forty-two days, respectively, of secondary postoperative complications. Two of the cases had no evidence of spread clinically or by repeated chest x-ray examinations. The third had a definite fatal contralateral infection and is discussed under "spreads."

In thirty-three of the forty-four cases, the instrument functioned satisfactorily as judged by complete bronchial occlusion, the production of atelectasis in the obstructed lobe or lobes, and the lack of a postoperative spread. Anesthesia has been definitely improved and, in general, the postoperative course of these patients has been smoother.

Spreads.—There were six cases in which contralateral spread occurred. One proved fatal, one was moderately severe, and the other four were all minimal.

The most severe spread occurred in a left pneumonectomy for tuberculosis; immediate postoperative x-ray views were clear, but on the fourth day, infiltration appeared in the right lower lobe and gradually progressed to involve the entire right lung, resulting in death forty-two days postoperatively. Although preoperative roentgenograms showed only diffuse scarring throughout the right lung, this might possibly be classified as a reactivation rather than a postoperative spread; the instrument functioned perfectly throughout the operation.

In one patient with multiple lung abscesses, it was felt that all cavitation was confined to the middle and lower lobes, and the balloon was inserted for a middle and lower lobectomy. The resulting contralateral spread from a cavity in the unobstructed upper lobe was moderately severe, but was relieved by bronchoscopy following the operation.

Of the four minimal spreads, two occurred in cases of tuberculosis, and there is no adequate explanation as to their cause. In the third case, a pneu-

monectomy for carcinoma, the instrument became lodged in a sharply curved endotracheal tube on removal, and several seconds elapsed before the bronchus was clamped. Sufficient spillage of secretions could have occurred to account for the small spread. In the last case, an abscess in the superior segment of the left lower lobe, the balloon was placed too low, and the superior branch bronchus was not obstructed.

Thus, of the six instances of spread, there is an explanation for three; the remaining three were all cases of tuberculosis.

Mechanical Complications.—Complications due to mistakes in technique occurred in five cases without evidence of postoperative spread. In two, the balloon was placed in the right main bronchus for a right pneumonectomy. Due to the extreme shortness of the right main bronchus, and because the balloon was placed too close to the carina, there was overdistention into the trachea with resultant partial obstruction, and it was necessary to remove the balloon. There were two left pneumonectomies for tuberculosis, in both of which there was extensive hyperplastic tissue filling the left main bronchus. It was realized that the balloon would probably not be retained in this hyperplastic tissue, but the presence of large amounts of purulent material in the stenosed lung necessitated its use. In each case, the balloon slipped out into the trachea during manipulation of the lung; tracheal obstruction was only momentary and was immediately relieved. No complications arose in the one case, but in the other, after removal of the balloon, the patient had sudden cardiac arrest during hilar manipulation and quickly died. An autopsy could not be obtained. The fifth and last case concerned an abscess in the superior segment of the right lower lobe; the balloon was placed too low, as denoted by the atelectatic basilar segments and inflated superior segment. The resulting spillage was removed by repeated tracheobronchial aspiration; fortunately a spread did not occur.

COMMENTS

Judging from the results up to the present time, certain conclusions can be drawn. The results in all types of cases are comparable except for tuberculosis. By improving the technique of handling the instrument and thus eliminating the complications which have occurred in this series, it is felt that the danger of spread in bronchiectasis, abscess, and bronchiogenic carcinoma with secondary suppuration may well be minimized.

The three unexplained spreads occurred in cases of tuberculosis, and were part of a group of six patients in whom streptomycin was not used. In the remaining nine cases, streptomycin was used both pre- and postoperatively, and spread did not occur. A much larger series of cases may afford some clue as to the mode of spread in tuberculosis.

In regard to the site of placement of the balloon in the bronchial tree, satisfactory positioning for lower lobectomy on either side, for resection of the middle and lower lobes on the right, and for pneumonectomy on the left is relatively simple. It is somewhat more difficult to block the superior branch bronchus of the lower lobes, as evidenced by failure in two of the twenty-one lobectomies.

Blocking the entire right main bronchus between the upper lobe orifice and the main carina is considerably harder, and should not be attempted without experience with the instrument. Placement of the balloon in two of the six right pneumonectomies was unsuccessful.

Experience with the instrument has shown that attention to the following details will decrease the chance of failure. Enforced postural drainage just prior to bronchoscopy has obviously facilitated this procedure. It is wise to institute suction through the balloon as soon after placement as possible, otherwise thick secretions may obstruct the aspirating tip before atelectasis is obtained. On removing the balloon the bronchus should be clamped as quickly as possible to prevent any spillage of dammed-up purulent material. Furthermore, thorough tracheobronchial suction should be carried out at the same time to catch any material which might spill out.

SUMMARY

An instrument designed for endobronchial occlusion and the results of its use in the first forty-four cases of resection for suppurative pulmonary diseases are reported. The results are sufficiently encouraging to warrant further clinical trial.

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DISCUSSION

DR. J. C. TRENT, Durham, N. C.—I should like to thank Dr. Moody for a very ingenious bit of work and an excellent presentation of this problem today. The instrument has been in use in Duke Hospital for the past two years and I can say that it does work. Complete occlusion of the bronchus can be produced, the balloon remains in place and will retain secretions, and in addition does produce atelectasis as shown in the movie. This greatly simplifies the surgeon's job. The upper lobe may be inflated, the dissection of the hilum is simplified, the postoperative course is smoother, and I think the addition of the use of this balloon for bronchial obstruction will improve the clinical results, especially when used in combination with streptomycin in tuberculosis.

DR. MOODY.—I should like to make sure that it is clear that this instrument is not applicable in upper lobectomies. It has been designed for lower lobectomies or pneumonectomies. The instrument designed for an upper lobectomy has not yet been completed.

I am particularly gratified to learn of the results achieved with streptomycin. We are becoming much more cognizant of the fact that contralateral spread does not always occur by way of the transbronchial rote. We have occluded the main bronchus in a number of cases of tuberculosis and several controlateral spreads have developed in spite of the fact that the instrument was functioning satisfactorily throughout the operative procedure.

MEDULLARY PEGGING IN THORACOTOMY INCISIONS

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COLUMBUS, OHIO

THE prerequisite of a good thoracotomy incision is adequate exposure not only of the immediate intrathoracic operative area, but also of the entire pleural space, which is particularly important in the presence of pleural adhesions. Good visualization of the entire intrathoracic structures and a large enough thoracotomy opening to allow free surgical manipulation are essential for a safe and rapid operative procedure. Equally important requirements of a thoracotomy incision are ease of closure with the production of a pain-free, stable hemithorax permitting full respiratory movement, minimal disturbance in the function of the shoulder, and, last but also important, good cosmetic results. The position of the patient on the operating table during the surgical procedure should also be considered and should not interfere with maximum function of the contralateral lung.

With the exception of inadequate exposure for certain posterior mediastinal lesions, the anterolateral incision as originally used by Rienhoff[1] meets most of the requirements of a good thoracotomy. The supine position interferes very little with the respiratory movement of the contralateral thorax and flooding of this lung can be prevented by frequent tracheal aspiration. The submammary incision will give excellent cosmetic results and section of the pectoralis major at its insertion will produce minimal damage to this muscle and its nerve. In young patients a third intercostal incision alone carried to the posterior axillary line will give excellent exposure with the use of a good spreading rib retractor. In older individuals the intercostal incision is usually combined with section of the costal cartilages of the third and fourth ribs. Overspreading of the rib retractor will lead to fractures of the adjacent ribs and for this reason when a larger thoracotomy is desired, additional cartilages should be sectioned. The repair of an anterior intercostal incision can be accomplished without difficulty by first approximating and suturing the sectioned costal cartilages. For airtight closure, if necessary, the pectoralis major muscle can be used for reinforcement of the intercostal suture line. Resection of a rib in an anterior thoracotomy is not advisable since this will make closure of the incision quite difficult due to the marked thinness of the anterior portion of the intercostal muscles. The anterior thoracotomy incision without resection of a rib will produce a stable thorax with minimal disturbance in respiratory movement. Postoperative pain is prevented by novocain injection or crushing of the third or adjacent intercostal nerves.

The posterolateral incision as first used by Lilienthal[2] is preferred by many to the anterior incision. This incision when used with either a high or low

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intercostal thoracotomy will give access to the upper or lower portion of the thorax as well as to the posterior and anterior mediastinum. It is particularly adapted for surgery on the esophagus, the vagus and sympathetic nerves, and the diaphragm. The lateral position of the patient on the operating table in this type of thoracotomy will somewhat interfere with respiratory movement of the contralateral hemithorax, unless shoulder and pelvic supports are used. A special table has been devised by Overholt[3] to overcome this difficulty. Preoperative use of antibiotics parenterally and by aerosol together with bronchoscopic aspiration has greatly reduced the hazards of contralateral lung flooding during resection of suppurative lung lesions. However, frequent tracheal aspiration during the operation and the Trendelenburg position will minimize this danger.

The skin incision is made starting at the level of the third or fourth rib, midway between the spine and the vertebral border of the scapula, and carried downward encircling the tip of the scapula and continuing along the seventh or eighth interspace to the anterior axillary line. The trapezius and rhomboideus muscles are cut close to the spine while the latissimus dorsi and serratus anterior are sectioned at least 6 cm. inferior to the tip of the scapula. Section of these muscles close to their insertion will produce minimal interference with postoperative movement of the shoulder.

Identification of the ribs in the posterolateral incision is greatly simplified by elevating the scapula and counting the ribs from above downward, the first rib being easily identified by its flatness and sharp ridge of the inferior border. The attachment of the posterior scalenus muscle to the second rib identifies this structure. For operations in the upper thorax the thoracotomy is accomplished through an intercostal incision in the fourth or fifth interspace, while for lower lobectomy and operations on the lower esophagus and diaphragm the incision can be made in the eighth or ninth interspace. An intercostal incision without section or resection of ribs, if carried forward anteriorly to the costal cartilage, frequently will give adequate exposure in young individuals. However, in older individuals and also in patients with marked thickening of the parietal pleura, the intercostal incision alone will not give sufficient exposure and overspreading of the rib retractor often will lead to fracture of ribs. The advantages of an intercostal incision without rib section are that it will allow easy closure of the thoracotomy, and deformity as such is absent. With crushing of one intercostal nerve, postoperative pain will be minimal and there will be very little interference with normal respiratory movements.

Resection of the major portion of a rib from its angle to the anterior axillary line or the costal cartilage with an incision through the periosteal bed is frequently used in the posterolateral thoracotomy. The exposure resulting from such thoracotomy may be inadequate in older individuals, in patients with thickened pleura, and in operations upon the esophagus. The removal of one rib creates a definite depression deformity which is particularly evident when used in the lower thorax. Closure of such thoracotomy is facilitated by the presence of the fascia-like structure of the periosteum of the resected rib;

however, considerable force is necessary to approximate the edges of this incision. With paralysis of the two adjacent intercostal nerves by novocain injection or crushing, there is minimal interference with respiratory movement.

An intercostal incision combined with section of two or more adjacent ribs will produce adequate exposure for all intrathoracic operations. However, on closure of this thoracotomy considerable difficulty is experienced in approximating the sectioned intercostal muscles requiring the use of sutures encircling the two adjacent ribs.[4, 5] Unless these sutures are placed subperiosteally, postoperative pain may occur due to pressure of the suture on the intercostal nerve of the inferior rib. Immobilization and accurate approximation of the cut ribs cannot be obtained by suture of the intercostal muscles to the longissimus

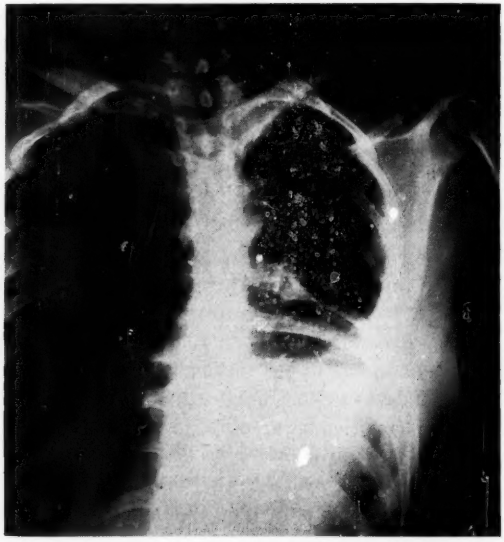

Fig. 1.—Thoracic deformity and excessive callus formation due to failure of accurate approximation of the sectioned rib fragments.

dorsi and iliocostalis muscles. Blades and Kent[6] advised the use of sutures placed through drill holes of the ends of the sectioned ribs. Unless the cut rib ends are approximated accurately and held in place firmly, the negative intrathoracic pressure will produce overriding of the rib fragments and the anterior rib segment is displaced posteriorly for a considerable distance, resulting in a thoracic depression deformity of considerable magnitude, particularly when two or more ribs are involved (Fig. 1). Constant movement of the rib ends and overriding with impingement of the intercostal nerves leads to considerable postoperative pain, particularly when nonunion of the sectioned ribs occurs. Crushing of the intercostal nerves, and particularly Novocain injection, will not be effective since union of the ribs does not occur for several months and may not occur at all. Irregular union with excessive callus formation greatly contributes to late postoperative pain (Fig. 2).

The prerequisite of a good thoracotomy incision has been met in this series in fifty patients by the use of the posterolateral intercostal incision and autogenous medullary pegging of the adjacent sectioned ribs. The exposure was adequate in all cases and suture of the intercostal muscles was accomplished with ease, without the use of a rib approximator or rib encircling sutures. There was minimal interference with respiratory movement of the thorax and deformities did not occur. Early unrestricted shoulder movement was possible and the cosmetic results were good. There was minimal postoperative pain, requiring only occasional use of narcotics. Ambulation on the first postoperative day was the rule and the postoperative hospital stay was short. The average hospital stay in twenty-four patients following lobectomy for bronchiectasis, decortication, and removal of mediastinal tumors was eight days. No atelectasis occurred.

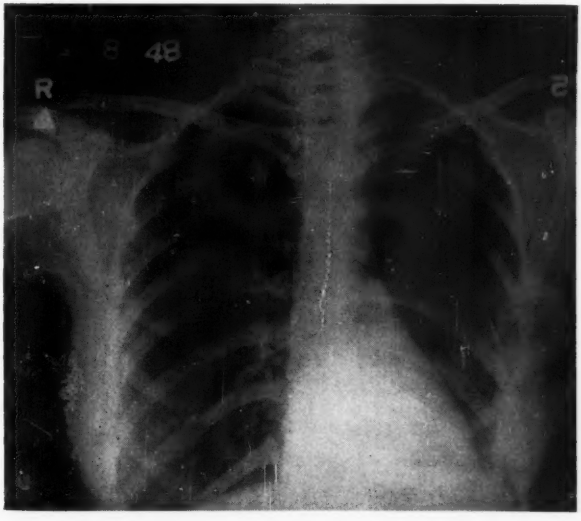

Fig. 2.—Overriding of the sectioned rib fragment and failure of regeneration of the resected rib with marked lateral thoracic deformity.

The usual posterolateral skin incision is used with section of the extrathoracic muscles close to their insertion. The longissimus dorsi and iliocostalis muscles are stripped from the ribs adjacent to the intercostal incision down to the transverse processes and retracted medially. A 1 cm. area of the periosteum is stripped from the two adjacent ribs 2 cm. distal to the transverse processes and the two ribs are transected without the removal of a segment (Fig. 3). The intercostal nerves of the corresponding ribs are exposed and crushed or injected with Novocain. The intercostal vessels above the intercostal incision are ligated with transfixation sutures and cut. Transection of two ribs usually gives excellent exposure; however, more can be cut should a wider exposure be desirable. On completion of the intrathoracic operation a 4 cm. long, 4 mm.

wide diamond-shaped section of the inferior border of the lateral portion of the rib above or below the intercostal incision is resected subperiosteally. The periosteum of this area is closed with interrupted fine silk. The removed section of rib is cut diagonally into two 3 cm. long, pointed cortical bone pegs which are inserted into the medullary cavity of the proximal rib stumps. On approximating the anterior rib segment to the proximal stump the sharp protruding peg

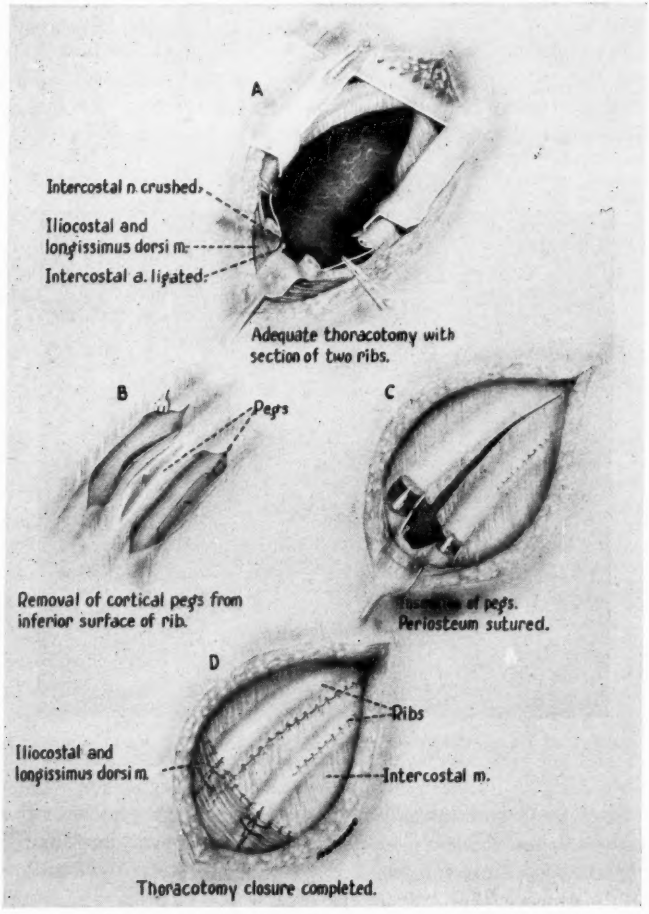

Fig. 3.—Technique of medullary pegging of ribs in thoracotomy.

will enter the medullary cavity and lock the rib in place (Figs. 4 and 5). The longissimus dorsi and iliocostalis muscles are next sutured to the intercostal muscles and for additional stability a suture may be placed encircling the distal portion of the rib firmly holding it in place. The intercostal muscles are next approximated by using interrupted sutures of fine silk. The cut segments of

Fig. 4.—Immediate postoperative position of the sectioned ribs.

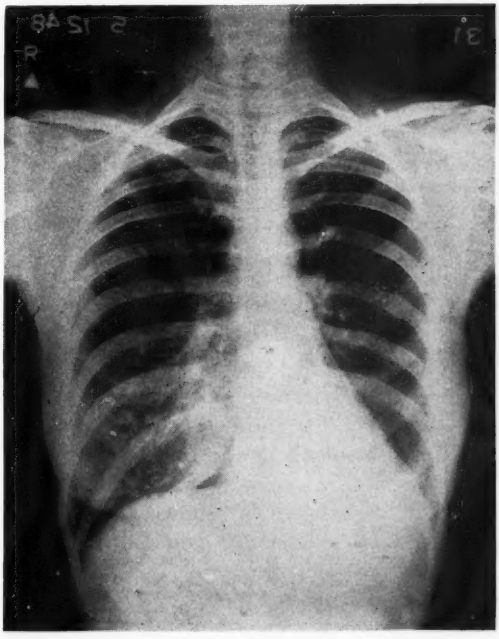

Fig. 5.—Bony union of the rib segments with minimal callus formation.

TABLE I. INTRATHORACIC OPERATIVE PROCEDURES USING MEDULLARY PEGGING OF RIBS

Lobectomies	24*
Pneumonectomies	6
Decortication	6†
Removal of mediastinal tumors	5‡
Exploratory thoracotomy	4
Esophageal operations	3
Patent ductus section	1
Closure of bronchial fistula	1
Total number of cases	50

*Two failures due to fracture of one peg.
†One failure due to fracture of one peg.
‡One failure, pegs too short.

the extrathoracic muscles are carefully approximated and sutured with interrupted silk. Interrupted silk is used for the skin.

In fifty thoracotomies performed for various surgical procedures as shown in Table I there were failures in four instances. In one patient with extensive carcinomatosis the ribs were extremely soft and an adequate bone peg could not be obtained. In one patient early in this series the pegs were too short and both ribs became disengaged. In two patients there was fracture of one peg each occurring on the first postoperative day.

SUMMARY

Adequate exposure for intrathoracic operations using the posterolateral incision has been obtained by the use of an intercostal thoracotomy combined with section of the two adjacent ribs. The use of autogenous medullary rib pegs has greatly facilitated closure of the intercostal incision with the production of a pain-free, stable thorax.

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OBSTRUCTIVE PNEUMONITIS OF NEOPLASTIC ORIGIN

An Interpretation of One Form of So-called Atelectasis and Its Correlation According to Presence or Absence of Sputum

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THE increasing safety with which it is possible to remove a lung surgically has led to a heightened demand for more frequent and more nearly accurate preoperative diagnosis of cancer. Although the cytologic examination of sputum was well described by Dudgeon and Wrigley[1] in 1935, it was not widely accepted at that time. Until recent years, the cytologic diagnosis of carcinoma of the lung on the basis of examination of sputum and bronchial secretions was largely a curiosity, and there was little to be accomplished surgically once the diagnosis was made. Largely as a result of the changed attitude toward pulmonary surgery, there has been a rebirth of interest in the cytologic examination of sputum and bronchial secretions, with the general hope that cancer of the lung may be detected more frequently and earlier.

Our experience with cytologic examination of sputum and bronchial secretions has indicated that examination of one or the other of these materials alone is not adequate. We have conducted cytologic examinations of approximately 2,400 specimens of sputum and bronchial secretions, the vast majority of which have been specimens of sputum. In this group we have at present 225 positive results among individual patients. Some of these represent positive results concerning sputum alone, some represent positive results concerning secretions alone, but in the vast majority of instances, it was possible to obtain positive results concerning both sputum and secretions. Cytologic examination of sputum is further indicated because of its value in the detection of cancer of the lung. Our conclusions in respect to this method have been that examination of both secretions and sputum should be done. With this in mind, it becomes exceedingly important to know the factors responsible for the production of sputum.

NATURE OF STUDY

The value of cytologic examination of bronchial material in the diagnosis of cancer of the lung has been aptly demonstrated. We felt, therefore, that it was important to determine those factors which are responsible for the production of sputum and how early sputum was produced in a group of patients who had proved cancer of the lung.

We have, therefore, re-examined all the lungs or lobes of lungs removed because of a neoplasm at the Mayo Clinic from May 6, 1935, to July 1, 1947.

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Three groups of pulmonary neoplasm were excluded from this study: (1) hamartomas (which in our experience have not produced sputum), (2) endobronchial lipomas and similar lesions, and (3) carcinomatous bronchial cysts.

The examination included a careful gross inspection of not only the neoplasm but also of the nonneoplastic portion of the lung. Blocks were taken from both the neoplasm and the pulmonary tissue of the affected segment of the lung. Sections were cut from these blocks and hematoxylin and eosin stains were used. Special stains, particularly van Gieson, were used when indicated.

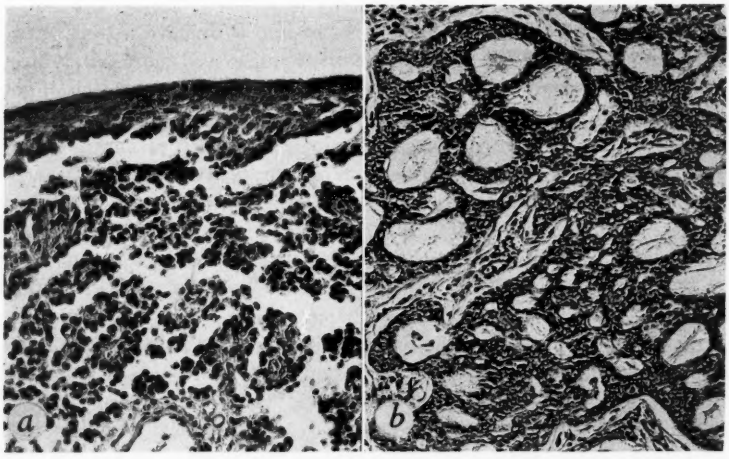

Fig. 1.—*a* (Case 27), Carcinoid type of adenoma of the left main bronchus: notice the intact benign epithelium overlying the tumor (×150); *b*, cylindroma type of adenoma in Case 23, from the left main bronchus: the Swiss-cheese pattern is apparent (×150). (Hematoxylin and eosin stain.)

All the tumors were classified into four groups: (1) adenoma of the carcinoid (Fig. 1, *a*) or cylindroma type (Fig. 1, *b*), (2) bronchiogenic carcinoma, (3) metastatic neoplasm, and (4) alveolar cell carcinoma. The bronchiogenic carcinomas were further classified into their cellular types: (1) squamous cell type (Figs. 2, *a* and *b*, and 3, *a*), in which the presence of keratinization, pearly bodies, or prickle cells was necessary, (2) undifferentiated large cell type, in which the cell type is large but there is no evidence of differentiation to squamous carcinoma or adenocarcinoma, (3) adenocarcinoma type, in which the neoplastic cells form mucus or acini, and (4) small or oat cell type (Fig. 3, *b*), in which the cells are small, round, or oval and contain little cytoplasm, and in which the nuclei have insignificant nucleoli.

The pneumonitis was graded according to a combination of the severity suggested by the microscopic picture as well as the gross extent of the process. Grade 1 pneumonitis indicates slight early pneumonitis, with very little areal involvement of the pulmonary tissue (Fig. 4, *a*) and grade 4 indicates very late, severe pneumonitis often involving a great extent of the lung (Figs. 4, *b* and 5, *a* and *b*). Grade 2 pneumonitis (Fig. 6, *a*) and grade 3 pneumonitis are

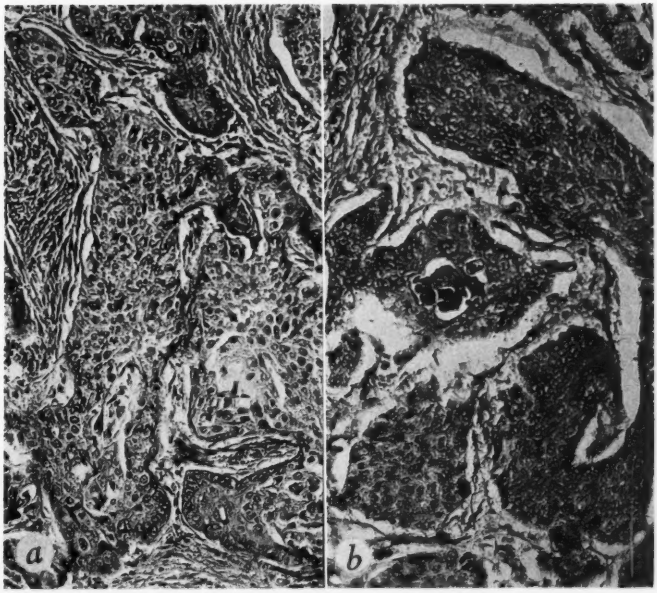

Fig. 2.—*a* (Case 65), Squamous cell type of bronchiogenic carcinoma of the main lower lobe bronchus (×15); *b*, squamous cell type of bronchiogenic carcinoma of the right lower lobe bronchus in Case 99 (×150). (Hematoxylin and eosin stain.)

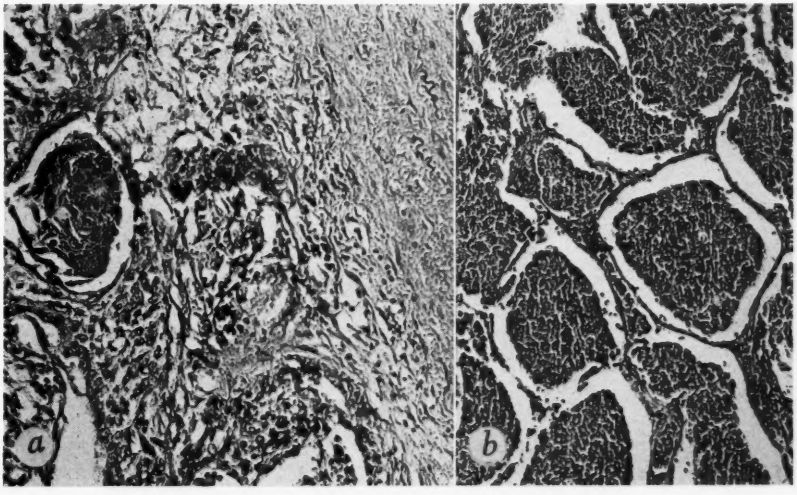

Fig. 3.—*a* (Case 62), Squamous cell type of bronchiogenic carcinoma of the right lower lobe bronchus, showing marked necrosis which is evidenced by the loss of all cellular detail; the voluminous amount of sputum raised by this patient (Table IV) was the result of evacuation of this necrotic material into the bronchial tree (×150); *b*, small or oat cell type of bronchiogeinic carcinoma of the upper left lobe bronchus in Case 171; the cells are small, round, or slightly elongated, and stain very deeply (×150). (Hematoxylin and eosin stain.)

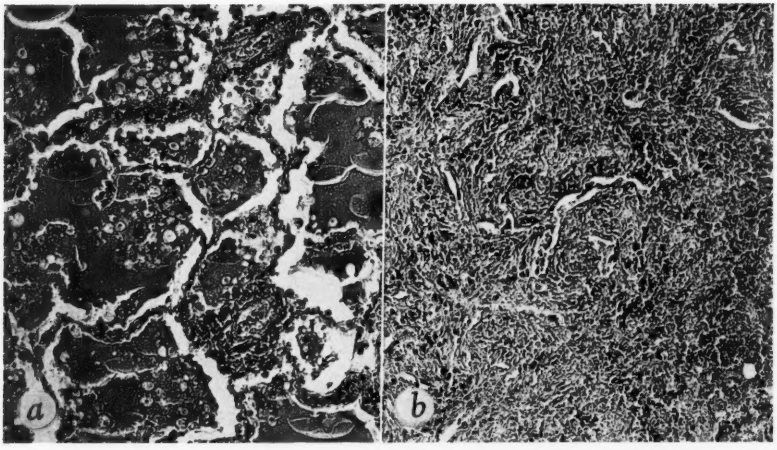

Fig. 4.—*a*, Early obstructive pneumonitis, in which the pulmonary alveoli are filled with edematous fluid; some polymorphonuclear leucocytes, lymphocytes, and phagocytes are present in the interalveolar septa and in the alveoli: this is an example of pneumonitis of grade 1 (×100); *b*, obstructive pneumonitis in the peripheral portion of the lung in Case 27 (see Fig. 1, *a*); notice the very marked fibrosis and the disappearance of the alveoli: this is an example of pneumonitis of grade 4 (×100). (Hematoxylin and eosin stain.)

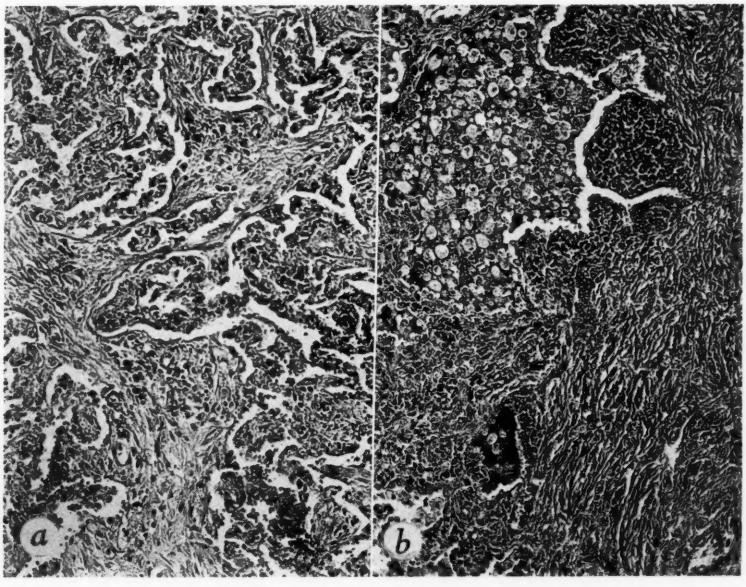

Fig. 5.—*a* (Case 99), Right lower lobe (see Fig. 2, *b*), showing pneumonitis of grade 4, with marked fibrosis and disappearance of the alveolar structure: notice the inflammatory cells (×100); *b*, section from the left upper lobe in Case 171 (see Fig. 3, *b*), showing pneumonitis of grade 4, with marked fibrosis: some fat-filled phagocytes are apparent, but no pulmonary alveoli can be seen (×100). (Hematoxylin and eosin stain.)

intermediate stages. In grade 1 pneumonitis it was possible to recognize the pulmonary alveoli; in grade 4 pneumonitis it was impossible to do so.

The records of these patients then were reviewed independently of the results of the gross and histologic examinations. Particular attention was accorded the presence or absence of sputum and, if sputum was present, the amount. The sputum was graded according to the volume. Hence, when very little (less than 1 ounce in twenty-four hours) was present, the sputum was graded 1; when 1 to 2 ounces in twenty-four hours was present, the grade was 2; when 2 to 3 ounces in twenty-four hours was present, the grade was 3; and when more than 4 ounces in twenty-four hours was present, the grade was 4.

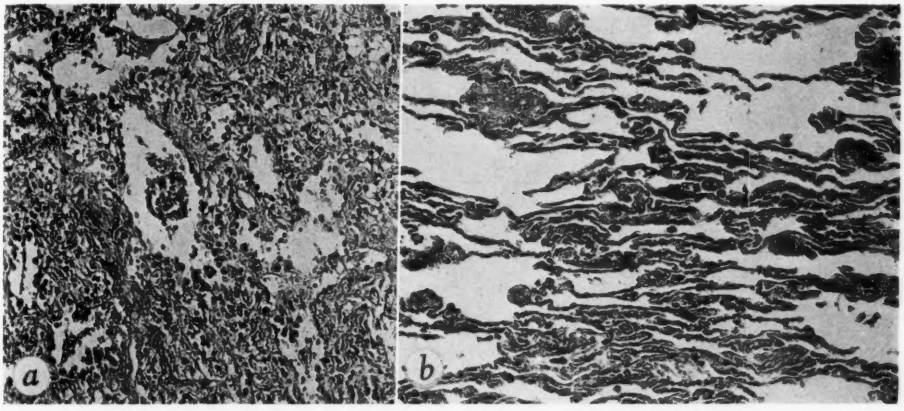

Fig. 6.—*a* (Case 23), Pneumonitis of grade 2 in the upper lobe; there is definite fibrosis, but a few remaining pulmonary alveoli can be seen (×100); *b*, section of atelectatic tissue in a case of hydrothorax: notice collapse of the pulmonary alveoli and the absence of any inflammatory reaction (×100). (Hematoxylin and eosin stain.)

DEFINITION OF TERMS

It became evident in this investigation that the lesion situated in the peripheral portion of the lung which drained into the affected bronchus was the factor which most frequently produced sputum. This is the lesion which roentgenologists in particular refer to as "atelectasis." Atelectasis is defined in Dorland's *American Illustrated Medical Dictionary* as either an "imperfect expansion of the lungs at birth," or as "partial collapse of the lung." The word derives from two Greek words meaning "imperfect expansion."

In medical literature, there are four different types of conditions in the lung which are referred to as "atelectasis." The one most acceptable is fetal atelectasis, in which there is failure of the lungs to expand at birth. The second type is the condition in which the lung is collapsed as a result of external pressure, such as hydrothorax (Fig. 6, *b*). The third is the condition known as "postoperative atelectasis," the histopathologic aspects of which are inadequately described because material is seldom available in the acute phase. The fourth is the condition under discussion herein, in which the lung becomes air-

less and becomes contracted after obstruction to the bronchus from varying causes, the main cause being, however, an obstructing neoplasm in the bronchus.

Since it appears to us that the genesis of these four conditions is different, we should like to abandon use of the term "atelectasis," at least as it refers to the peripheral pulmonary changes associated with obstructive lesions of the bronchus. As an alternative, we would suggest the term "obstructive pneumonitis." This would appear to be a better term for this condition than such terms as have been applied, in addition to "atelectasis." Such terms as "organizing bronchopneumonia," or "chronic interstitial pneumonia," "bronchiectasis," and "chronic indurative pneumonia," in our opinion, describe only part of the entire syndrome which we think should be designated as "obstructive pneumonitis."

Fig. 7.—Bronchiogenic carcinoma, squamous cell type, of the lower lobe bronchus. The obstructive jaundice in the lower lobe is evident. The bronchi are widely dilated, and contain secretions. The lobe has not contracted. This represents an early stage of obstructive pneumonitis.

GENESIS OF OBSTRUCTIVE PNEUMONITIS OF NEOPLASTIC ORIGIN

We should like to depict the various stages in the genesis of this condition when the cause of the obstruction is a neoplasm. In the early stages, the ob-

structive lesion produces a damming-back of secretions into the bronchi and even into the alveoli. In this stage the involved portion of lung usually is reddish. The bronchi are dilated and filled with mucus, and the alveoli are filled with mucus and serum. The serum apparently is an exudate from the capillaries. In this stage. there is no contraction of the involved portion of the lung (Fig. 7). Rather, it is more voluminous than normal. However, in this and subsequent stages the involved lobe or lung is airless. This condition has sometimes been referred to as "drowned lung." Inflammatory cells in the form of polymorphonuclear leucocytes, plasma cells, and lymphocytes can be found in this stage in the affected pulmonary tissue. In this and later stages it is frequently possible to demonstrate bacterial organisms. As the lesion progresses, it is often possible, moreover, to find areas of lipoid-filled phagocytes in the pneumonitic area. In a short time organization of the exudate ensues, which in several weeks leads to the formation of collagen which becomes more marked as the time interval increases.

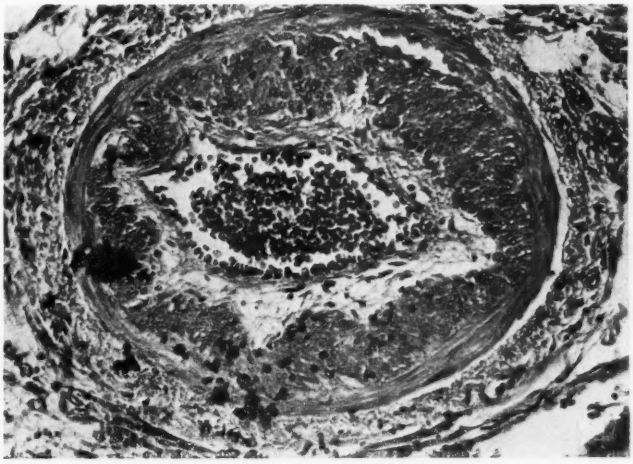

Fig. 8 (Case 88).—Pulmonary arteriole in a section of lung, showing advanced obstructive pneumonitis. Notice the marked intimal thickening with resulting narrowing of the lumen (hematoxylin and eosin, ×200).

The affected lung in the stage in which fibrosis is present shows remarkable changes in the pulmonary arteries and veins, particularly those of medium size and smaller ones. As the process progresses, endarteritis (Fig. 8) affects both the pulmonary arteries and veins in the lobe or lung. This may progress to complete occlusion of the vessel. The process apparently is only an expression of the lack of function of the lobe, with the diminished need for blood. This condition might well be called "physiologic endarteritis." It occurs in the vessels to any organ which ceases to function.[2] One of the best examples outside the lung is the kidney.

In the lung, this condition of course leads to contracture of the lobe (Fig. 9). Grossly, the affected lobe in this stage is firm, and brownish or gray, with

thickening of the overlying visceral pleura. Less commonly, the pneumonitis progresses to formation of abscesses (Fig. 10). When abscesses form, they are no different from other pulmonary abscesses. They may break through to the pleura and lead to empyema, with bronchopleural fistula. Since the neoplasm which is the cause of the bronchial obstruction is not static, there are bronchi which have been obstructed more recently than others. As a result, there is considerable variation in the age of the pneumonitic process. We believe that it is the mucopurulent fluid accompanying pneumonitis which forms most of the sputum in the majority of patients who have neoplasms of the bronchus.

Fig. 9 (Case 171).—Small or oat cell type of bronchiogenic carcinoma of the upper lobe bronchus (see Figs. 3, *b* and 5, *b*). There is marked chronic obstructive pneumonitis, with contracture. The thickening of the visceral pleura overlying the pneumonitic process is evident.

Occasionally, obstructive pneumonitis was present although the neoplasm had not completely obstructed the bronchus. Indeed, in some cases there was a very adequate airway. Nevertheless, there must be, in such cases, physiologic block to the egress of secretions, whether this block is brought about by replacement of ciliated columnar cells by carcinoma cells, which obviously are incapable of ciliary action, or by a splinting of the wall of the bronchus, the result of infiltration by the neoplasm. The occurrence of obstruction in spite of a patent lumen is seen in the common bile duct in carcinoma of the duct.

At what stage in the production of obstructive pneumonitis can the affected lung return to a normal or near normal state, provided the obstructing lesion is removed? At present this question is impossible to answer. Isolated cases in our series would suggest that once the obstruction has been removed, many

of these lungs affected by obstructive pneumonitis will clear up. The following case illustrates this point.

REPORT OF CASE

A 36-year-old man came to the clinic complaining of a cough productive of one-half cup of sputum. Associated with the cough were chills and fever. These symptoms had been present for one year. A roentgenogram was reported as showing slight atelectasis of the left lung. Bronchoscopy revealed a neoplasm of the left main bronchus. This lesion histologically proved to be an adenoma of carcinoid type. The endobronchial portion of the tumor was removed. Cough and sputum disappeared entirely, and the roentgenogram one year later was reported as disclosing nothing abnormal. One year and five months later the lung was removed surgically. Grossly, there was no evidence of pneumonitis in the left lung, although there was a residual adenoma in the main bronchus which did not produce obstruction.

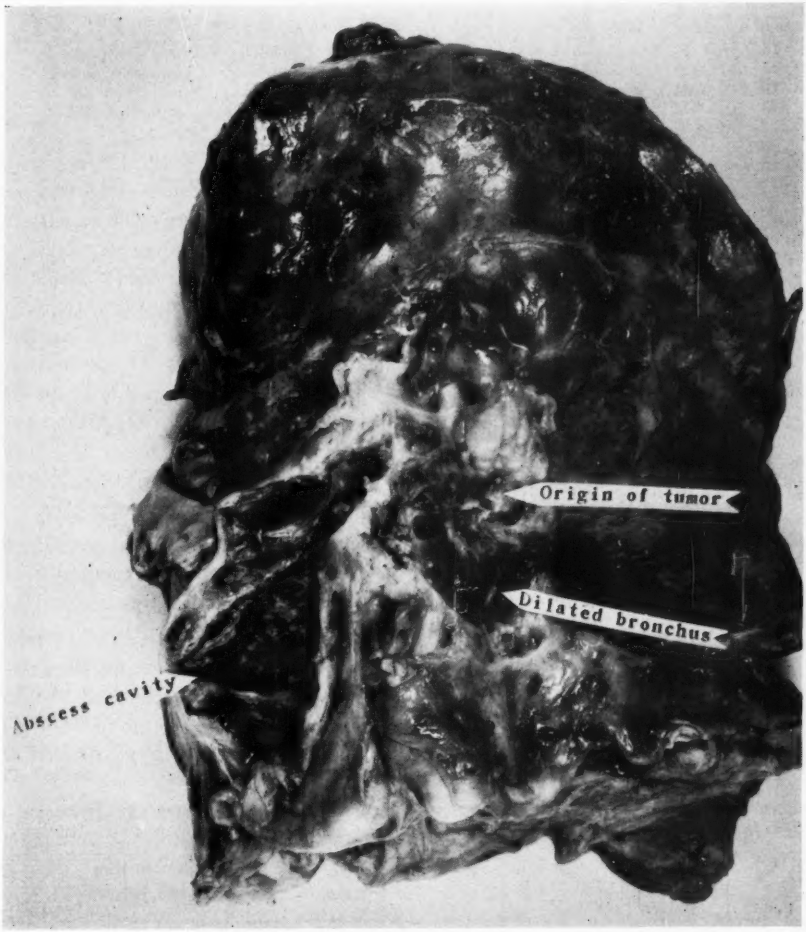

Fig. 10 (Case 27).—Carcinoid type of adenoma of the left main bronchus (see Figs. 1, *a* and 4, *b*). Chronic obstructive pneumonitis involves the entire lung. An abscess cavity is situated beneath the pleura, in the lower lobe.

TABLE I. PRESENCE OR ABSENCE OF SPUTUM, GRADE OF PNEUMONITIS, AND SITUATION OF TUMOR IN NEOPLASTIC OBSTRUCTIVE PNEUMONITIS; NEOPLASM: ADENOMA OF BRONCHUS

CASE	SEX	AGE (YR.)	TUMOR LOCATION, BRONCHUS	PNEUMONITIS, GRADE, LOBE	SPUTUM, QUANTITY
1	F	46	L main	0	0
2	F	43	LUL	0	0
3	M	46	RLL	0	0
4	F	45	RUL	0	0
5	M	23	LLL	0	0
6	M	43	LLL	0	0
7	F	61	RML	0	0
8	M	36	LUL	0	0
9	M	17	RUL (peripheral)	0	0
10	M	42	L main	0	0
11	F	36	R main	0	0
12	M	48	RLL*	1 RLL	1
13	M	49	LUL	1 LUL	2
14	F	22	RLL	2 RLL	3
15	F	41	LUL	3 LUL	4
16	M	18	RUL	3 RUL	2
17	M	47	RLL	3 RLL	2
18	F	41	RLL	3 RLL	3
19	F	31	LLL	3 LLL	3
20	M	19	R main	3 RLL	3
21	M	46	RLL	3 RLL, RML	4
22	M	36	L main*	3 L lung	4
23	F	39	L main*	3 LLL, 2 LUL	2
24	M	30	L main	4 LUL	3
25	F	59	LLL	4 LLL	4
26	F	23	L main	4 L lung	4
27	M	29	L main	4 L lung	4
28	F	40	LLL	4 LLL	4
29	F	42	RLL	4 RLL	4
30	M	31	RUL	4 RUL	2
31	M	22	R main	4 RML & RUL	4
32	M	15	R main	4 RUL, 2 RML	4
33	F	39	LUL	4 LUL	3
34	M	46	RLL	4 RLL	4
35	F	25	RLL	4 RLL	3
36	M	30	RLL	4 RLL	4
37	M	30	RLL	4 RLL	1

*Cylindroma type; others are carcinoid type.

AGE AND SEX OF PATIENTS AND DISTRIBUTION OF TYPES OF LESIONS

Twenty-one of the 37 patients who had adenomas (Table I) were males, a percentage of 56. The 2 patients who had alveolar cell carcinoma were females (Table II). Six of the 14 patients who had metastatic malignant processes were males (Table III). One hundred seven of the 118 patients who had bronchiogenic carcinomas (Tables IV, V, VI, and VII) were males, an incidence of 91 per cent. The youngest patient with an adenoma was 15 years old; the

TABLE II. PRESENCE OR ABSENCE OF SPUTUM, GRADE OF PNEUMONITIS, AND SITUATION OF TUMOR IN NEOPLASTIC OBSTRUCTIVE PNEUMONITIS; NEOPLASM: ALVEOLAR CELL CARCINOMA

CASE	SEX	AGE (YR.)	TUMOR LOCATION, BRONCHUS	PNEUMONITIS, GRADE, LOBE	SPUTUM, QUANTITY
38	F	34	LLL (peripheral)	0	0
39	F	57	Entire LLL	0	1

TABLE III. PRESENCE OR ABSENCE OF SPUTUM, GRADE OF PNEUMONITIS, AND SITUATION OF TUMOR IN NEOPLASTIC OBSTRUCTIVE PNEUMONITIS; NEOPLASM: METASTATIC LESIONS

CASE	SEX	AGE (YR.)	TUMOR LOCATION, BRONCHUS		PNEUMONITIS, GRADE, LOBE	SPUTUM, QUANTITY
40	M	36	RLL*		0	0
41	F	33	LUL (peripheral)	D	0	0
42	M	33	RUL (peripheral)	B	0	0
43	F	20	RLL (peripheral)	B	0	0
44	F	51	LUL (peripheral)	A	0	0
45	M	37	RLL (peripheral)	A	0	0
46	F	50	R main	A	0	0-1
47	F	67	L (lung, peripheral)	E	0	1
48	F	54	LLL (peripheral†)	A	0-2	1
49	M	47	LUL (peripheral)	A	1 LUL	1
50	M	38	RUL	C	2 RUL	2
51	F	36	R (lung, peripheral)	E	2	2
52	F	38	R main	A	3 RLL	3
53	M	28	R main	F	3 R lung	3

*Cylindroma primary in trachea.
†Areas of necrosis in tumor.
A, Adenocarcinoma.
B, Fibrosarcoma.
C, Osteogenic sarcoma.
D, Chorionepithelioma.
E, Lymphosarcoma.
F, Grade 4 teratocarcinoma.

oldest was 61 years old; the average mean age was 36.6 years. Among those who had bronchiogenic carcinomas, the youngest patient was 28 years old; the oldest was 69 years old; the average age was 54.1 years. Among the patients who had a metastatic malignant process, the youngest patient was 20 years old; the oldest, 67 years old; the average age was 41.1 years. Of the entire group of neoplasms, 21 per cent were adenomas, 69 per cent were bronchiogenic carcinomas, 8 per cent were metastatic malignancies, and 1 per cent alveolar cell carcinomas. Of the bronchiogenic carcinomas, 47 per cent were the squamous cell type, 27 per cent were the indeterminate large cell type, 9 per cent were the small or oat cell type, and 17 per cent were the adenocarcinoma type.

CORRELATION BETWEEN THE AMOUNT OF OBSTRUCTIVE PNEUMONITIS AND SPUTUM

It is apparent, from an examination of the tables, that there is a very high degree of correlation between the amount and degree of obstructive pneumonitis and the amount of sputum. The fact that sputum is present when a patient has an adenoma as well as when a patient has a bronchiogenic carcinoma is evidence that the replacement of the normal bronchial mucosa with carcinoma, which occurs with remarkable consistency in bronchiogenic carcinoma, is seldom a factor by itself in the production of sputum (Fig. 11, *a* and *b*). Nonneoplastic benign mucosa overlies bronchial adenoma, with the exception of periods in which the patient is bleeding. Except for transient periods, ulceration of the benign mucosa does not overlie the adenoma.

Sputum was present in 26 of the 37 patients who had adenomas and absent in 11, or 29 per cent (Table I). It is misleading to say that a patient never has sputum, because most persons at one time or another can raise secretions from their bronchial trees in the form of sputum, and we are certain that although there were patients who said they did not have sputum, many had minimal amounts at irregular intervals.

TABLE IV. PRESENCE OR ABSENCE OF SPUTUM, GRADE OF PNEUMONITIS, AND SITUATION OF TUMOR IN NEOPLASTIC OBSTRUCTIVE PNEUMONITIS; NEOPLASM: BRONCHIOGENIC CARCINOMA, SQUAMOUS CELL TYPE

CASE	SEX	AGE (YR.)	TUMOR LOCATION, BRONCHUS	PNEUMONITIS, GRADE, LOBE	SPUTUM QUANTITY
54	M	53	L main	0	0
55	M	58	L main	0	0
56	M	44	L main	0	0
57	M	57	RUL	0	0
58	M	58	LUL	0	0
59	M	54	RLL	0	0
60	M	52	RUL	0	0
61	M	53	L main	0	1
62	M	55	RLL*	0	4
63	M	51	RUL	0-3 RUL	1
64	M	57	RLL	0-4 RLL	2
65	M	59	RLL	1	1
66	M	55	LUL	1 LUL	2
67	M	66	LUL	1 LUL	1
68	M	40	L main	1 LLL	1
69	M	60	R main	1 RLL	1
70	M	66	RLL	1 RLL	1
71	M	60	RML	1 RML	1
72	M	59	⅔ L lung	1 LUL	3
73	M	41	LUL	1 LUL	1
74	M	55	RLL*	1 RLL	4
75	M	49	RLL	2 RLL	2
76	M	43	RUL	2 RUL	2
77	M	55	RML	2 RML	1
78	F	58	LUL	2 LUL	1
79	M	44	RLL	2 RLL	3
80	M	54	LLL	2 LLL	2
81	M	62	RLL	2 RLL	3
82	M	54	RLL	3 RLL	4
83	M	46	RLL	3 RLL	2
84	M	60	LLL	3 LLL	2
85	M	61	RUL	3 RUL	4
86	M	48	RLL	3 RLL	2
87	M	51	RLL	3 RLL	2
88	M	60	RLL	3 RLL	4
89	M	52	RLL	3 RLL	3
90	M	55	RUL	3 RUL	4
91	M	55	L main	3 L lung	4
92	M	48	LUL	3 LUL	4
93	M	64	RLL	3 RLL	2
94	M	50	L main	4 LUL	4
95	M	48	RLL	4 RLL	4
96	M	44	RUL	4 RUL	2
97	M	52	LUL	4 LUL	4
98	M	62	LLL	4 LLL	4
99	M	62	RLL	4 RLL	3
100	F	52	R main	4 RLL	4
101	M	69	LUL	4 LUL	3
102	M	49	LLL	4 LLL	4
103	M	48	LLL	4 LLL	3
104	M	51	LLL	4 LLL	2
105	M	39	LUL	4 LUL	3
106	M	57	RLL	4 RLL	4
107	M	50	RUL	4 RUL	4
108	M	56	RLL	4 RLL	3

*Central necrosis of tumor.

TABLE V. PRESENCE OR ABSENCE OF SPUTUM, GRADE OF PNEUMONITIS, AND SITUATION OF TUMOR IN NEOPLASTIC OBSTRUCTIVE PNEUMONITIS; NEOPLASM: BRONCHIOGENIC CARCINOMA, INDETERMINATE LARGE CELL TYPE

CASE	SEX	AGE (YR.)	TUMOR LOCATION, BRONCHUS	PNEUMONITIS, GRADE, LOBE	SPUTUM, QUANTITY
109	F	58	LUL	0	0
110	M	55	LUL	0	0
111	M	38	R (superior sulcus)	0	0
112	M	54	RUL (peripheral)	0	0
113	M	57	LUL	0	0
114	M	57	LUL	0	0
115	F	50	RUL (peripheral)	0	0
116	M	55	RLL (peripheral)	0	0
117	M	51	Entire RML	0	0
118	M	37	Entire RUL	0	0
119	M	43	LUL (peripheral)	0	0
120	M	64	RLL (peripheral)	0	0
121	M	59	LLL	0	0
122	F	28	L main	0	0
123	M	60	RLL (peripheral)	0	0
124	F	50	LLL (peripheral)	0	0
125	M	58	RLL (peripheral)	0	0
126	M	56	RUL	0	0-1
127	M	50	LUL (peripheral)	0	0-1
128	M	56	RUL (peripheral)*	0	1
129	M	46	LUL*	0	1
130	F	60	RLL (peripheral)*	0	1
131	M	66	RUL (peripheral)*	0-2 RUL	1
132	M	64	L main	1 LLL	1
133	M	64	L main	1-3 L lung	1-2
134	M	33	RUL	1 RUL	1
135	M	62	RLL	2 RLL	2
136	M	59	R main	2 RUL, 3 RLL	4
137	M	56	RUL	2 RUL	1
138	M	52	LLL	3 LLL	3
139	M	51	LLL	3 LLL	3
140	M	48	LUL	3 LUL	2

*Central necrosis of tumor.

TABLE VI. PRESENCE OR ABSENCE OF SPUTUM, GRADE OF PNEUMONITIS, AND SITUATION OF TUMOR IN NEOPLASTIC OBSTRUCTIVE PNEUMONITIS; NEOPLASM: BRONCHIOGENIC CARCINOMA, ADENOCARCINOMA TYPE

CASE	SEX	AGE (YR.)	TUMOR LOCATION, BRONCHUS	PNEUMONITIS, GRADE, LOBE	SPUTUM, QUANTITY
141	F	58	RUL (peripheral)	0	0
142	M	60	RUL (peripheral)	0	0
143	M	40	LUL (peripheral)	0	0
144	M	64	RUL	0	0
145	M	57	L main	0	0
146	M	54	LLL (peripheral)	0	0
147	F	58	RUL (peripheral)	0	0
148	M	63	RLL (peripheral)	0	0
149	M	51	RLL	0	0
150	F	50	LUL (peripheral)	0	0
151	M	55	LLL (peripheral)*	0	1
152	M	58	RLL (superiorly)†	0	2
153	M	60	LLL	0-3 LLL	2
154	M	49	LUL (peripheral)	1 LUL	1-4
155	M	38	R main	2 RLL	3
156	M	57	RLL	2 RLL	2
157	M	59	RLL	2 RLL	1
158	M	60	LUL	3 LUL	3
159	M	47	R main	3 R lung	4
160	M	37	R main	4 R lung	4

*Central necrosis of tumor. †Pulmonary infarction.

TABLE VII. PRESENCE OR ABSENCE OF SPUTUM, GRADE OF PNEUMONITIS, AND SITUATION OF TUMOR IN NEOPLASTIC OBSTRUCTIVE PNEUMONITIS; NEOPLASM: BRONCHIOGENIC CARCINOMA, SMALL OR OAT CELL TYPE

CASE	SEX	AGE (YR.)	TUMOR LOCATION, BRONCHUS	PNEUMONITIS, GRADE, LOBE	SPUTUM, QUANTITY
161	M	49	RUL (peripheral)	0	0
162	M	56	LUL	0	0
163	M	66	RLL	0	0
164	M	54	LUL	1 LUL	1
165	F	45	LLL	1 LLL	1
166	M	56	R main	1 RLL	1
167	M	48	R main	1 RLL	1
168	M	56	RML	2 RML	2
169	M	52	L main	3 LLL	2
170	M	56	RLL	3 RLL	2
171	M	53	LUL	4 LUL	4

Of 2 patients who had alveolar cell carcinoma (Table II), one gave no history of sputum and the other gave a history of minimal amounts of it.

Thirty-seven, or 31 per cent, of 118 patients who had bronchiogenic carcinoma gave no history of sputum (Tables IV, V, VI, and VII). Among the several types of bronchiogenic carcinoma, it is evident that the more peripheral the situation of the carcinoma tended to be, the less was the chance for the development of sputum. This was particularly true of the adenocarcinoma type of lesion and of the large cell indeterminate type. The reason for this, it would

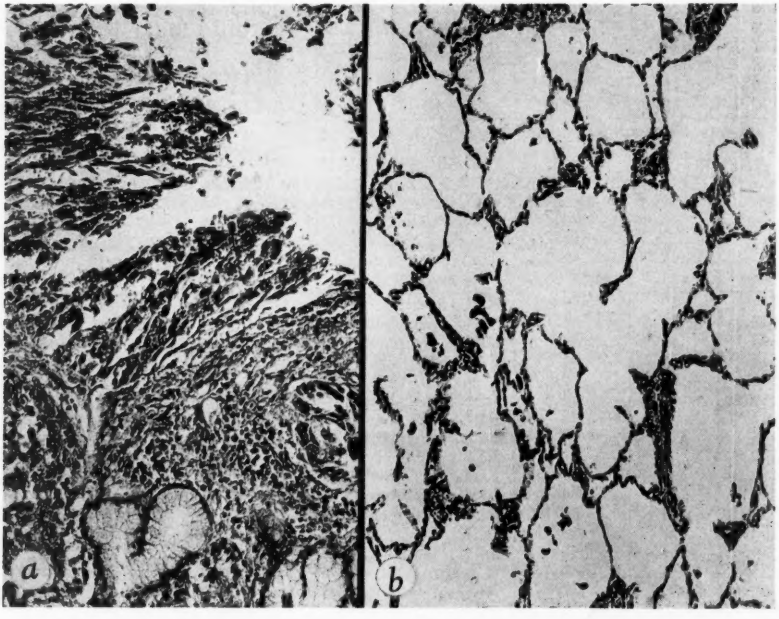

Fig. 11 (Case 61).—*a*, Squamous cell bronchiogenic carcinoma of the left main bronchus: the normal bronchial mucosa is replaced by carcinoma (×150); *b*, the peripheral pulmonary tissue in the same case is normal (×100). (Hematoxylin and eosin stain.)

seem, is that these lesions tend to be more peripherally situated than do the other types of bronchiogenic carcinoma, and this peripheral location means that the chance of their obstructing a larger bronchus and producing obstructive pneumonitis is diminished.

In the group of 14 patients who had metastatic neoplasms, 6 had no sputum (Table III).

Fig. 12 (Case 62).—A large, squamous cell type of bronchiogenic carcinoma of the right lower lobe (see Fig. 3, *a*), with massive necrosis and cavitation of the central portion of the tumor. The necrotic central portion of this tumor was the factor which produced copious sputum in the patient (Table IV).

In a small percentage of cases, there was not an absolute correlation between the quantity of sputum and the severity of obstructive pneumonitis. It was felt that when lack of correlation did occur, it frequently could be explained on the basis of central necrosis of the tumor (Figs. 12 and 3, *a*). In such instances, the neoplasm was large and the central portion of the tumor had undergone necrosis and had evacuated through a bronchus, producing sputum.

This evacuation of the necrotic center of the tumor produces an excavating carcinoma. The onset of sputum, under these circumstances, usually is sudden, and the sputum itself is voluminous. It is noteworthy that such evacuation did not occur in association with any of the adenomas which, because of their slow growth, as a rule do not exhibit necrosis. In one instance (Case 117) there was infarction of nonneoplastic peripheral pulmonary tissue, which it was felt accounted for the production of sputum.

We are unable to find any correlation between (1) the presence or absence of sputum and the amount of sputum with (2) the duration of symptoms. We considered the possibility that the presence or absence of sputum and the amount of sputum might depend, to some extent, on whether the lesions were situated in the upper or lower lobe, inasmuch as there is more dependent drainage from the upper lobe. This did not prove to be the case.

Certain patients who had bronchiogenic carcinoma do not have any sputum, and in such cases if the carcinoma is inaccessible bronchoscopically, the only way to obtain cellular proof of the carcinoma is to examine secretions removed bronchoscopically. However, as has been stated, it is our feeling that many patients who have cancer of the lung can produce a small amount of sputum which may be adequate for cytologic examination. It would appear that the presence of measurable amounts of sputum, since it is dependent upon pneumonitis, is not an early symptom of primary carcinoma of the lung.

SUMMARY

We have described the histopathologic changes in the periphery of the lung secondary to an obstructing neoplasm of the bronchus.

It was felt that it would be more nearly accurate to term this condition "obstructive pneumonitis" rather than the commonly employed term, "atelectasis."

We have shown that there is a very high degree of correlation between the presence of this type of pneumonitis and the presence of sputum.

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(See discussion on page 122.)

CYTOLOGY OF BRONCHIAL SECRETIONS

Its Role in the Diagnosis of Cancer

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THIS discussion attempts to present the experience of the clinician and the surgeon with the method of cellular study of bronchial secretions in relation to the diagnosis of cancer, and to evaluate statistically our findings with those previous reports on this topic which have come for the most part from the cytologist, the pathologist, or the endoscopist.

Papanicolaou, who has done so much to establish on a sound footing the cell smear method of diagnosing cancer, has himself pointed out that there is nothing new in this method, and the historical fact is that the examination of body fluids for the detection of cancer cells dates back to the nineteenth century. Beale (1860), Sanders (1864), Quincke (1875), and Hampeln (1876) succeeded in identifying cancer cells in sputum. Dudgeon and Wrigley of England (1935), and Wandall of Denmark (1944) have reported good results in their examination of sputum smears for neoplastic cells.

On June 22, 1945, the first sputum specimen in the series under discussion was smeared and studied at New York Hospital. The material was from an obscure case of Cromwell's, in which there was a clinical suspicion of cancer of the lung. The patient had a serosanguineous sputum and the x-ray findings were suggestive. The sputum smears were not particularly good and disclosed nothing unusual except for one group of cells with enlarged heterogeneous and hyperchromatic nuclei. These were diagnosed as a group of malignant cells and the subsequent bronchoscopy revealed no definite endobronchial changes, but at thoracotomy, a nonresectable lung cancer was revealed. A mediastinal node excised at this time proved the growth to be an undifferentiated type of bronchiogenic carcinoma.

CLINICAL MATERIAL

Following this initial success, it soon became evident that a detailed cytologic study of sputa and bronchial secretion obtained from a large number of persons afflicted with a variety of pulmonary and bronchial diseases would be necessary before the differential, diagnostic value of the smear procedure in the detection of pulmonary cancer could be determined.

Bronchial secretions or sputa have been studied in a series of 1,200 cases, and the number of specimens studied for each patient varied from one to seven. A majority of the earlier patients, however, suffered from inflammatory lung conditions rather than cancer, and so for the clinical portion of

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this report we took 400 consecutive cases on record at Memorial Hospital from June, 1945, to January, 1948. Having been hospitalized at Memorial Hospital, there was at least some clinical suspicion of cancer in most of these patients.

TECHNIQUE

One of the chief factors which had in the past prevented this diagnostic method from acquiring the credit it actually deserved was, first, a lack of an adequate, simple, and uniform technique for preparation of material, and second, a scarcity of personnel trained in the interpretation of the smeared cells. Four years ago, through the work of Papanicolaou, such a technique became available and the interest and confidence of medical men in this diagnostic procedure has markedly increased since then.

For a sputum examination, material is requested after coughing, and this is collected and fixed immediately in 70 per cent alcohol. Three twenty-four hour specimens are routinely ordered. Smears are made and fixed in alcohol-ether. All smears are stained first in hematoxylin and then in OG6 and EA65. A good nuclear staining is essential. The two counter stains used are fairly transparent and give a good differentiation of basophilic and acidophilic cells. Eosin is not recommended as a counter stain because it is less transparent and stains all cells uniformly.

The technique for obtaining material for cytologic study by bronchial washing and aspiration is essentially that which is recommended by Dr. Louis H. Clerf. At bronchoscopy we carry out the following steps: (1) A suitable cannula is introduced through the bronchoscope into the suspected branch bronchus. (2) Then the patient is turned until the suspected portion of lung is dependent. (3) A syringe containing 2 to 5 c.c. of sterile normal saline is attached to the cannula and the fluid slowly injected. (4) The patient is then shaken gently and we wait about three minutes before (5) attaching the collection bottle to the cannula. (6) Suction is applied while the patient is turned back to elevate the suspect portion of lung above the cannula tip. The collected material is placed in a bottle containing 70 per cent alcohol.

CLASSIFICATION (PAPANICOLAOU)

Cytology reports are returned to us from the laboratory grouping the specimens into five classes. Briefly, a Class I specimen is negative for cancer cells, Class II is suggestive, Class III is suspicious, Class IV is strongly positive, and the Class V specimens show conclusive evidence of bronchiogenic cancer.

From the surgeon's standpoint, this classification is a bit cumbersome. It would seem that a biopsy or sample should be reported either as cancer or as negative for cancer. The Class III reports, however, do have the virtue of tending to stimulate and urge the clinician to send more samples for study.

ADVANTAGES AND DISADVANTAGES

Among the advantages of this diagnostic test may be mentioned: (1) Its simplicity and inexpensiveness. (2) Its reliability in the hands of experienced cytologists. (3) It permits the early recognition of incipient cases or of hid-

den carcinomas, such as cancer in situ, because it is known that aberrant cells are exfoliated from the surface of a carcinoma even before it becomes ulcerated. (4) The test can be carried out on a large scale as a screening method. (5) It does not conflict in any way with other well-established methods of pathologic diagnosis, but on the contrary proves a valuable complement to them as it covers a larger area than they do. (6) It may reveal the presence of a cancer not discovered by bronchoscopy and biopsy. (7) It is of unique value in following up the results of operative procedures and the progress of radiation or mustard gas therapy.

Its main disadvantages are: (1) Its criteria need further standardization. (2) The type and origin of the malignant cells are not always clear. (3) It does not show the grade of the malignancy. (4) It does not supply information as to the mitotic activity of the malignant growth or its relationship to the adjacent normal tissues. (5) It does not give the location of the cancer in the tracheobronchial tree. In this connection it should be noted that Herbut reported he is able to recognize three more or less separate groups of cancer cells in bronchial secretions: (1) clusters of cells which are present in cases of squamous cell carcinoma, (2) large irregular single cells found in the more undifferentiated tumors and in those with an adenomatous formation, and (3) smaller, more uniform cells present in the so-called oat-cell carcinoma. Papanicolaou has not so classified our specimens, but has been content to report on the presence or absence of cancer cells.

FALSE POSITIVE DIAGNOSES

In the over-all group of 1,200 cases there have been four false positive reports. In three instances the specimen came from a patient subsequently found to have bronchiectasis, and restudy of these false positive smears has revealed cytologic features characteristic of this type of pulmonary disease which now permits their differentiation from the cells found in bronchiogenic cancer. The confusing cells were probably fragments of papillomatous growths of the bronchial mucosa such as have been previously described in cases of bronchiectasis. The true nature of these cell clusters is now recognized and no false positive reports have occurred in recent cases of bronchiectasis. In the Memorial Hospital series of 400 cases there were no false positives, and in no case reported as Class V (positive for cancer) has the diagnosis as yet been clinically disproved. There are, however, several patients with such reports on whom the final histologic proof of bronchiogenic cancer has not yet been substantiated either by surgery or autopsy.

TABLE I

Proved bronchiogenic cancer		236
Operations		74—31%
Exploratory thoracotomy	48	
Pneumonectomy	21	
Lobectomy	5	
Resections based on positive cytology		7

Seven resections of lung were carried out on the basis of a cytology report positive for cancer.

In each of 18 cases in which operation has been undertaken on the basis of a Class V cytology report, the diagnosis has been confirmed. At Memorial Hospital 7 pneumonectomies have been correctly undertaken when the only positive preoperative histologic evidence to justify the procedure was a Class V report on sputum or bronchial washing.

In the present series of 236 bronchiogenic cancers, there have been 141 positive reports (Classes IV and V), giving an accuracy rate of 60 per cent.

TABLE II

Cases studied	400	
Proved bronchiogenic cancer	236	
Positive sputa	112	60%
Positive bronchial aspirate	27	

The percentage of accurate positive reports in the recent cases is nearly 90 per cent.

CASE REPORTS

CASE 1.—W. M., a man, 56 years of age, complained of chest pain of eight months' duration, a chronic cough, profuse sputum, and fourteen pounds loss of weight. Physical examination revealed suppressed breath and voice sounds of the right lower chest.

X-ray Report.—X-ray examination showed segmental atelectasis of the paravertebral segment of the right lower lobe with no definite clue from the films as to the etiology. An endobronchial tumor as well as bronchiectasis had to be considered as possibilities. Bronchoscopic examination was advised in view of the possibility of bronchiogenic cancer.

Bronchoscopy.—Bronchoscopy findings were entirely negative.

Bronchial Washings.—There was conclusive evidence of a malignant neoplasm, most likely a bronchiogenic cancer, Class V.

Gross Specimen.—The right lung was removed by pneumonectomy. On the lateral posterior portions of the lower lobe the pleura was puckered and a nodule was palpable beneath it. At the bifurcation of the right lower lobe bronchus a creamy white, firm, infiltrating tumor was noted. Distal to this the lung tissue was firm and on section the bronchi and bronchioles were dilated and contained yellowish-green, thick, puslike material. Sections through the posterolateral portion of the lower lobe showed multiple areas of firm, yellowish-gray tissue lying immediately below the pleura and surrounded by nonerepitant dirty, gray-brown lung tissue. At the point where the cancer began in the bronchus there was a 1½ cm. node, and in the hilus there were four soft nodes.

Microscopic Study.—Bronchiogenic epidermoid carcinoma, grade II, was found. The extrapulmonary nodes showed no tumor. Bronchopulmonary nodes were positive for cancer.

CASE 2.—D. W., a man 50 years of age, complained of a slight cough. He gave a history of having had virus pneumonia in August, 1947, and again in December, 1947. January, 1948, Monilia were found on pure culture. Physical examination revealed moist râles in the right posterolateral base of the lung and an old right apical tuberculosis.

X-ray Report.—In the right lower lung field, there was a two-inch patch of infiltration with ill-defined borders. There were a few productive, tuberculous changes in the right infraclavicular region. Findings seemed most consistent with an inflammatory process.

Bronchoscopy.—Findings at bronchoscopy were entirely negative.

Bronchial Washings.—There was conclusive evidence of a malignant neoplasm. Malignant cells were numerous, Class V.

Gross Specimen.—The specimen consisted of the entire right lung. In the apex were two firm, partly calcified nodules. The upper and middle lobes were otherwise normal and the upper portion of the lower lobe was not remarkable. The basal portion of the lower lobe was almost completely replaced by a large moderately firm tumor mass measuring 11 by 10 by 8 cm. It was smooth, firm, pinkish-yellow in color and extended to the visceral pleura

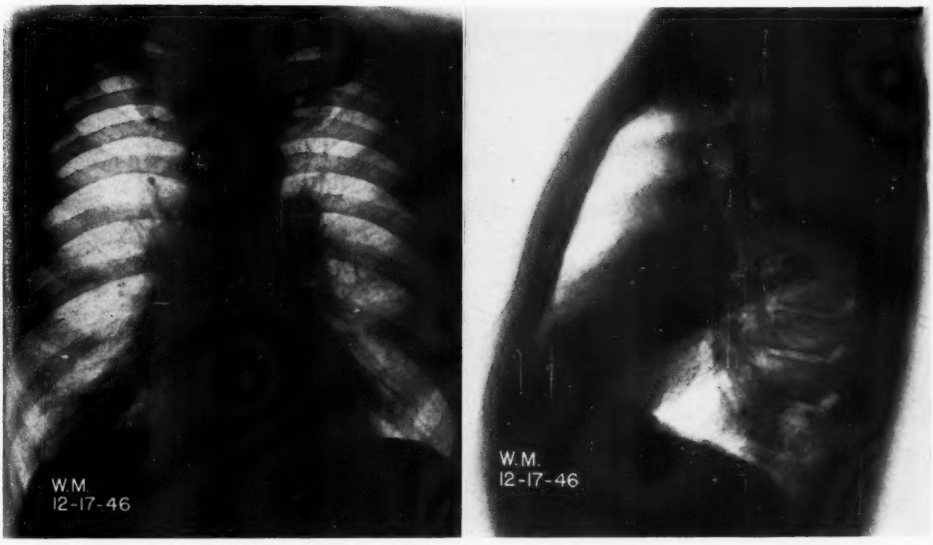


Fig. 1 (Case 1).—Chest radiographs showing segmental atelectasis of the paravertebral segment of the right lower lobe.

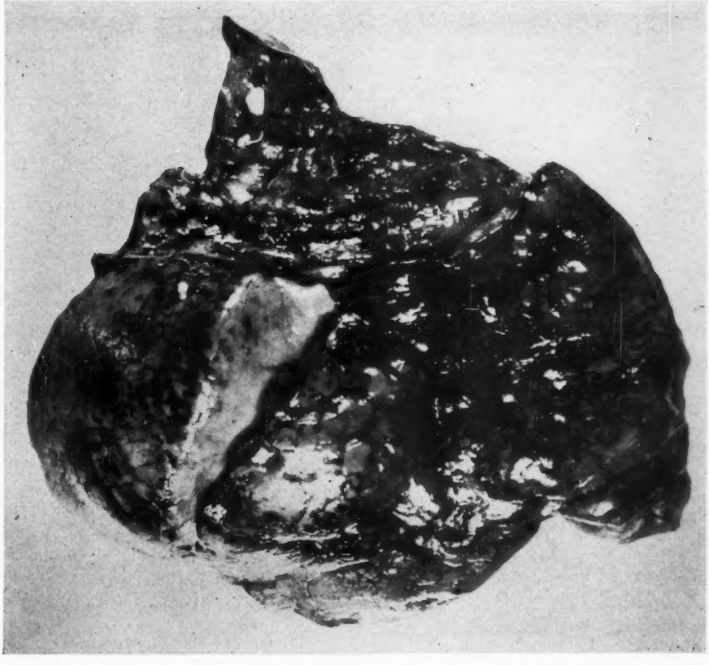
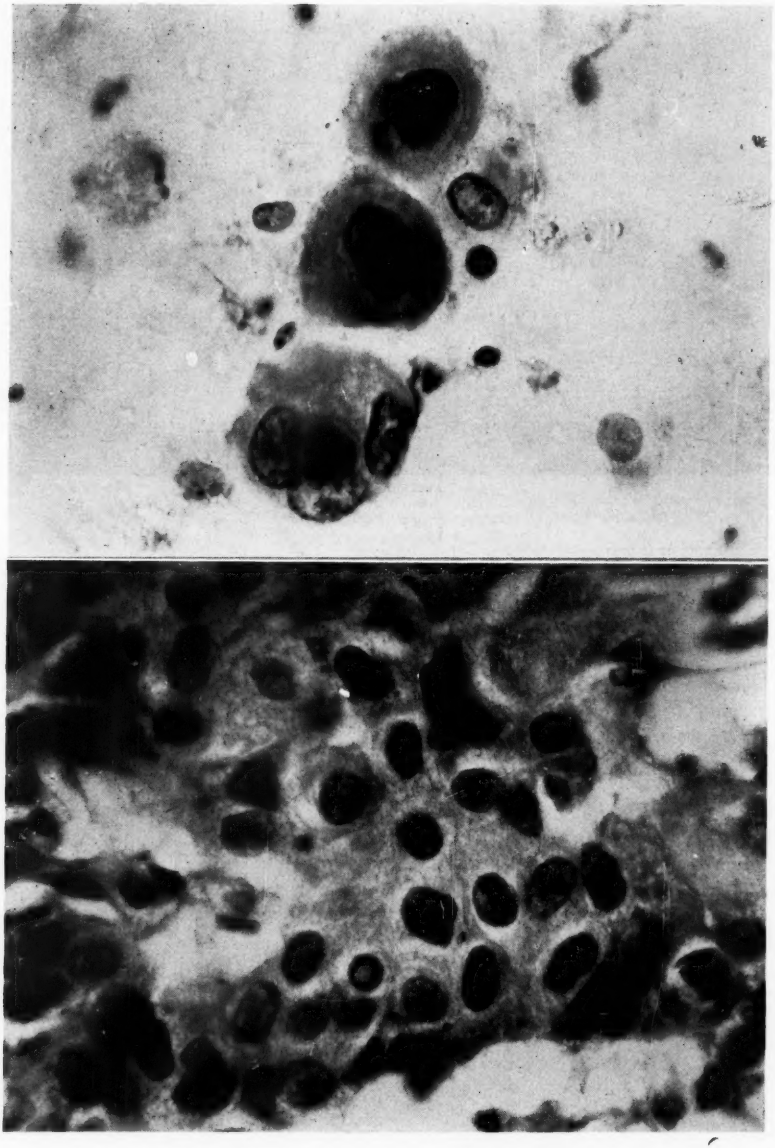


Fig. 2 (Case 1).—Gross specimen consisting of the entire right lung. It reveals an early cancer of the lateral, posterior portion of the lower lobe with surrounding pneumonitis and abscess formation. The middle and upper lobes are inflated.

A.



B.

Fig. 3 (Case 1).—*A*, Bronchial washing specimen showing cancer cells, Class V. *B*, Formal histologic section of the operative specimen showing epidermoid carcinoma, Grade II.

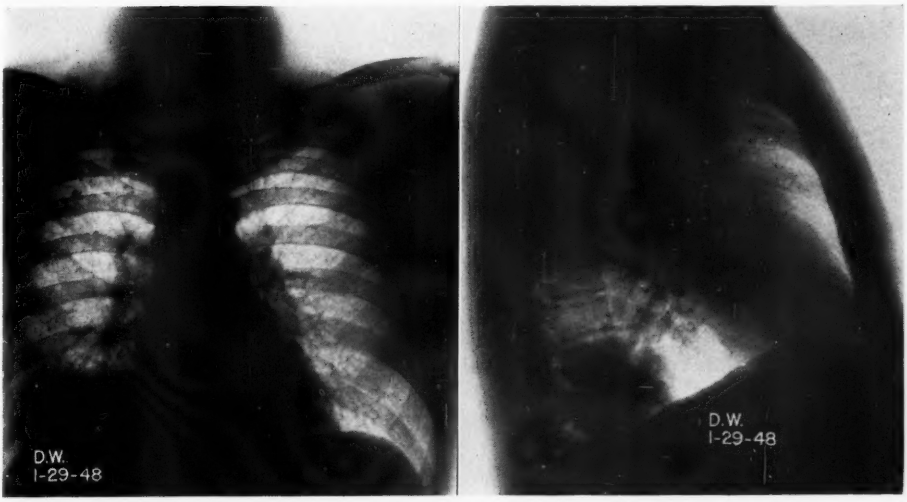


Fig. 4 (Case 2).—Chest radiographs showing a 6 cm. patch of infiltration with ill-defined borders in the right lower lung field thought to be consistent with an inflammatory process.

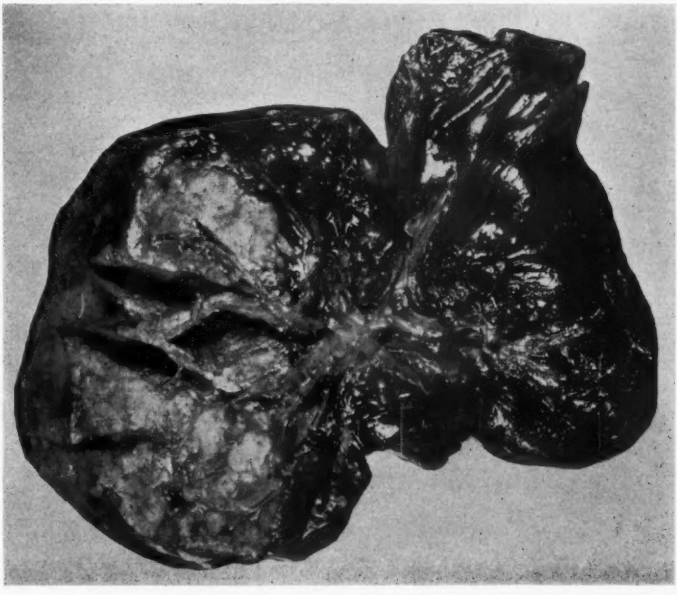
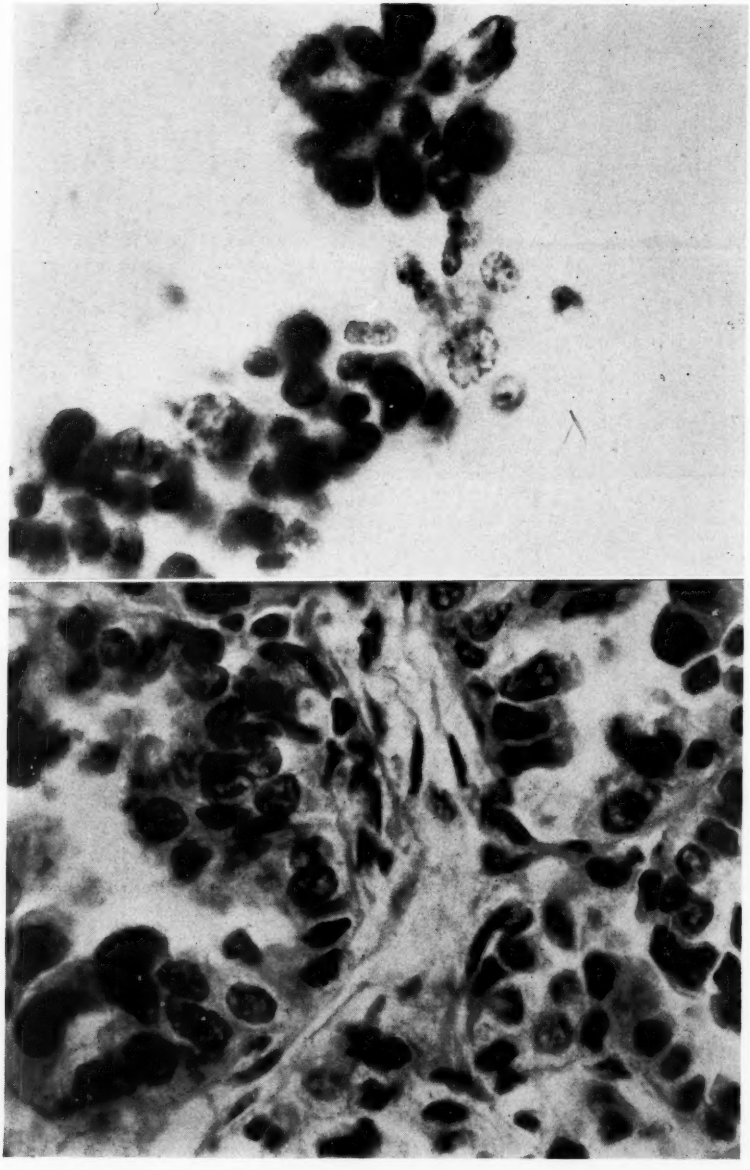


Fig. 5 (Case 2).—Gross specimen consisting of an entire right lung. The basal portion of the lower lobe is almost completely replaced by tumor but without ulceration of bronchus or bronchioles.

A.



B.

Fig. 6 (Case 2).—*A*, Bronchial washing specimen showing conclusive evidence of bronchiogenic cancer, Class V. *B*, Formal histologic section of the operative specimen showing peripheral bronchiolar carcinoma of lung, grade II. It has some papillary and pseudoglandular features.

over a wide area. Distinct subpleural nodules similar to the main tumor were seen nearby, but there was no ulceration of the bronchus or bronchioles.

Microscopic Study.—Carcinoma of the lung, grade II, peripheral bronchiolar type having papillary and pseudoglandular features was reported. About the main tumor were multiple satellite tumor bodies. It could not be ascertained whether these represented multicentric primary growths or whether their source was from the main bulk of the tumor. Two hilar nodes showed metastatic cancer.

COMMENTS AND CONCLUSIONS

The method of examination of sputa and bronchial secretions for cancer cells has become a routine with us in every case in which an intrathoracic neoplasm is suspected. It has become an additional, complementary, diagnostic measure. It is not a substitute for the already well-established and reliable methods previously used in establishing the diagnosis of lung cancer.

It is apparent, however, that cytologic studies will sometimes be the only way in which lung cancer can be definitely diagnosed prior to operation. Competent cytologists believe their positive smear diagnosis of pulmonary cancer is as trustworthy as that made by the pathologist from a study of a histologic section of tissue removed at biopsy. Many conscientious thoracic surgeons feel more confident about proceeding with radical surgery when a positive diagnosis has been established microscopically.

In our busy outpatient department, we find that cytologic studies tend to lessen the interval between the first clinic visit and admission to the hospital for surgical care. Because we have a limited inpatient bed capacity, the procedure has helped us to select suitable cases for admission and to cut down the number of days of hospitalization prior to surgery.

Four hundred consecutive admissions to Memorial Hospital were studied. There were 236 cases of proved bronchiogenic cancer. There were 112 positive sputum reports and 29 positive bronchial washings, a positive cytologic diagnosis in 60 per cent of the cases.

There were 176 bronchoscopies, and 63 positive biopsies were obtained (37 per cent); 98 aspiration biopsies were done and 85 positive reports returned (86 per cent).

TABLE III

Proved bronchiogenic cancer	236
Bronchoscopies	176
Positive bronchoscopic biopsy	63—36%
Aspiration biopsy of lung	98
Positive aspiration biopsy	85—86%

A positive bronchoscopic diagnosis of cancer was obtained in 36 per cent of the cases and 86 per cent of the aspiration biopsies of lung were positive.

Practically all of the patients in this series had had a recent diagnosis of pneumonia made by their family doctors. If the thoracic surgeon is to cure more patients with bronchiogenic cancer, he must have more early cases, and one way to get these early cases is for the internist to view with suspicion each case of "atypical pneumonia" in a patient over 35 years of age, and every patient with recurring "virus pneumonia" or "unresolved pneumonia" should

have a bronchoscopy and complete cytologic studies. A diagnosis of pneumonia probably is not justified if subsequent radiographs of the chest do not show the absence of pneumonia. Early cases will be found also on routine chest x-ray studies and mass survey.

Early, operable, and curable cases of bronchogenic carcinoma can be detected by cytologic measures.

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DISCUSSION ON "OBSTRUCTIVE PNEUMONITIS OF NEOPLASTIC ORIGIN" BY DR. JOHN MC DONALD, DR. STUART W. HARRINGTON, AND DR. O. THERON CLAGETT;* AND "CYTOLOGY OF BRONCHIAL SECRETIONS" BY DR. WILLIAM L. WATSON, DR. HENRY CROMWELL, DR. LLOYD CRAVER, AND DR. GEORGE N. PAPANICOLAOU

DR. JOHN H. GIBBON, JR., Philadelphia.—We have complete confidence in a diagnosis of cancer of the lung based upon the finding of neoplastic cells in the bronchial secretions. We reported upon this method last year before this Association. I was particularly pleased to hear Dr. Watson speak of false positive diagnoses. The method actually will be of little use if there is a false positive. Two years ago, we made one false positive diagnosis. This patient had a large pulmonary abscess and we did a pneumonectomy. We have had no false diagnoses since then.

I think it is only fair to the pathologists to say that they frequently need more than one specimen to make a positive diagnosis. Bronchoscopy has been done in some of our patients four or even five times before the pathologist has been able to find neoplastic cells in the bronchial secretions. Sometimes if there is adequate clinical evidence we operate without a positive tissue or cellular diagnosis.

The incidence of positive finding of neoplastic cells in the bronchial secretions is approximately 90 per cent, which is quite high. The incidence of positive tissue diagnosis is between 40 and 50 per cent. I think these two authors are to be congratulated on this very interesting addition to our diagnostic procedures in this disease.

DR. JOHN W. STRIEDER, Boston.—I should like briefly to record our experience at The Boston City Hospital. Dr. Donald McKay and Dr. Paul Ware have been working on this diagnostic method for three years and have examined more than 1000 smears. That does not mean 1,000 cases, but, as has been suggested, we believe that at least three readable smears should be examined before they are considered to be of diagnostic value for a given case. It is of interest to discuss the two methods (sputum and bronchial secretions), as to whether one or the other is of greater value in the study of exfoliated tumor cells. Perhaps both specimens should be used in the given case so that maximum diagnostic precision may result. Tumor cells in the sputum may come from the larynx or esophagus, but it should be simple to rule these tumors out. It is the late suppurative pulmonary lesion, that is frequently accompanied by roentgenographic change, in which diagnosis by sputum examination is easiest. I would like to mention the simplified method of obtaining bronchial secretions for smear by means of the aspirating tube that Dr. Ware has devised† and that is now being

*See page 97 for article by McDonald, Harrington, and Clagett.
†Now being manufactured by George P. Pilling & Son Co., Philadelphia, Pa.

made by Pilling. By means of this tube, secretions may be taken with considerable precision from a suspected zone in the bronchial tree.

Table I is a summary of 170 cases among which were 54 cases of bronchiogenic carcinoma.

TABLE I

Total number of bronchoscopic cases			170
Number of cases of bronchiogenic carcinoma			54
(a) Histologic diagnosis			48
(b) Clinical diagnosis			6
Positive smears (54 cases of carcinoma)			40 (74%)
False negative smears (Carcinoma present; smear negative)			14 (26%)
False positive smears (No carcinoma; smear positive)			3
Total number of errors			17 10%)
	Total smears	Positive	Negative
Bronchoscopy positive	29 (54%)	26 (48%)	3 (6%)
Bronchoscopy negative	25 (46%)	14 (26%)	11 (20%)
Total	54 cases	40 (74%)	14 (26%)

It will be seen that 6 cases of histologically unproved carcinoma are included in the 54. These seemed, clinically, to be unequivocal cases of bronchiogenic cancer and were included because they test the method under adverse statistical circumstances. If they are excluded, the percentage of positive smears (in 48 proved cases) rises to 83 per cent, and the positive bronchoscopic tissue diagnoses to 60 per cent.

DR. CLARENCE CRAFOORD, Stockholm.—The pathologists with whom we are working are always very cautious when stating whether or not cells in smears from the sputum are positive for malignancy. Because of that we have tried as far as possible to get bronchoscopic biopsy specimens for them. By using specially constructed bronchoscopic biopsy forceps the incidence of positive biopsies can be considerably increased. We now use flexible thin forceps with which we can go out into small bronchial branches with the guidance of x-ray in order to get small pieces of tissue from diseased areas. In many of these cases the biopsy is taken far beyond the field of vision in the bronchoscope. By this means we now have positive biopsy answers in about 80 per cent of our cases of carcinoma of the lung.

DR. McDONALD.—I had not intended to discuss the results that we have had in studying sputum and bronchial secretions for cancer cells, but I believe that a few words might be said. At the present time, we have had somewhat more than 200 cases in which we have made a positive diagnosis on the basis of sputum or bronchial secretions or both, and we feel gratified with the accuracy and results of this method of examination. We believe that it is a valuable diagnostic aid.

DR. WATSON.—I would like to say that each patient coming through our Thoracic Clinic has cytologic studies carried out on several sputum specimens while he is an outpatient, and when hospitalized and bronchoscoped the suspected bronchus is always washed with saline and the aspirated material studied for tumor cells. Bronchial washings may be positive before the patient has begun to produce enough sputum for study.

Cytology institutes and some private medical laboratories are now set up to study and report on sputum specimens sent in by the family doctor. This increase in the range of usefulness of the cytology method should lead to the discovery of unsuspected early bronchiogenic carcinomas suitable for surgery.

Each suitable patient suspected of having bronchiogenic carcinoma should have a bronchoscopy, and, if the diagnosis cannot be established by biopsy, a bronchial aspirate of the suspected bronchus should be obtained.

INTRATHORACIC MENINGOCELE

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CLEVELAND, OHIO

IT IS now accepted that surgical exploration and, if possible, extirpation is the treatment indicated for benign, malignant, and potentially malignant tumors and cysts of the mediastinum. Although the differential diagnosis of these lesions has increased in accuracy, occasionally involvement of the mediastinal lymph nodes by tuberculosis, Hodgkin's disease, or one of the lymphomas cannot be distinguished preoperatively. Usually this is of no consequence. A biopsy is taken at the time of exploration, the diagnosis is established, and treatment can then be started on a rational basis. However, any means by which differential diagnosis can be improved and unnecessary exploration can be avoided should be sought. For this reason and because of the rarity of the lesion, a case of mediastinal meningocele simulating mediastinal neurofibroma is reported.

CASE REPORT

C. T., a 40-year-old white woman, was admitted to the Thoracic Surgical Service of Cleveland City Hospital on Aug. 8, 1946, for treatment of an intrathoracic tumor first diagnosed in March, 1946, following a routine photo-fluoro-roentgen survey by the Cuyahoga County Tuberculosis Clinic. The patient had no symptoms at this time. In May, 1946, she developed mild attacks of dyspnea and substernal oppression lasting only a few hours. These attacks increased slightly in duration and severity during the next few months.

The significant findings on physical examination at the time of admission were numerous cutaneous and subcutaneous nodules and a few café au lait spots, all typical of generalized neurofibromatosis. The only other significant findings were confined to the radiologic examination of the chest and thoracic spine. X-rays of these areas as demonstrated in Fig. 1 (*A*, *B*, and *C*) showed a homogeneous ovoid mass in the right paravertebral gutter adjacent to the sixth, seventh, eighth, and ninth thoracic vertebrae and four 1.5 cm. circular defects involving the posterior portions of the bodies of these vertebrae and the regions of their spinal nerve foramina.

The tentative diagnosis was posterior mediastinal neurofibroma, probably multiple, involving the adjacent vertebrae with hourglass extension into the spinal nerve foramina. Neurological examination showed no evidence of intradural involvement. Reflexes, sensation, and muscle powers were normal throughout. Spinal fluid was normal as were the spinal fluid dynamics. In view of these findings, it was felt that an exploratory thoracotomy was indicated.

Operation.—On Aug. 12, 1946, under intratracheal anesthesia, a right posterolateral incision was made through the bed of the resected eighth rib and the tumor was exposed transpleurally. A cystic tumor, measuring 3 by 4 by 8 cm. and covered by parietal pleura, was found just lateral to the bodies of the sixth, seventh, and eighth thoracic vertebrae. It was apparent that the mass was not a neurofibroma, but that it communicated with the subarachnoid space of the spinal canal through one of the circular defects seen in the x-ray views. In attempting to free the cyst from the parietal pleura, the cyst was entered and several ounces of thin, clear, colorless, watery fluid escaped. The cyst was then widely opened and found to communicate through the enlarged seventh spinal nerve foramen with the spinal subarachnoid space. (Fig. 2.) A normal spinal cord and nerve roots could be seen in their usual positions. The defects in the other three adjacent spinal nerve foramina could be seen and felt. They were covered with parietal pleura which bulged moderately before the cyst was opened. These areas were not disturbed.

From the Department of Thoracic Surgery, Cleveland City Hospital, Western Reserve University.

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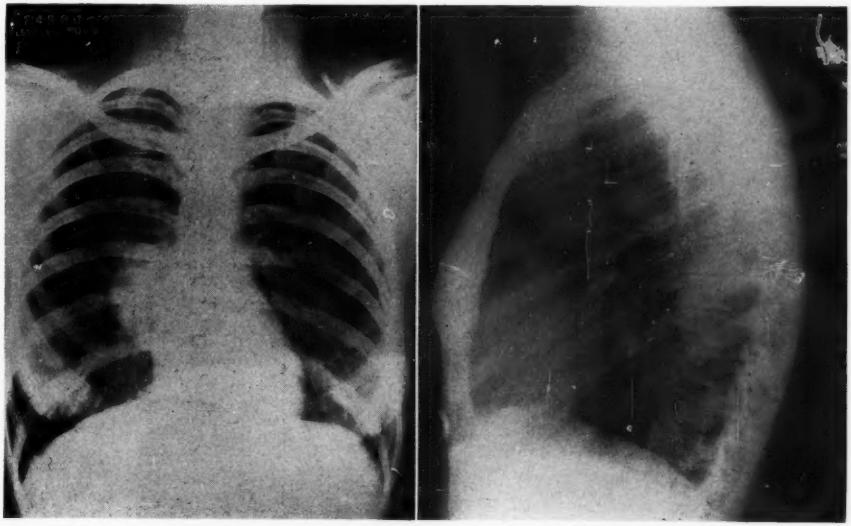
The cyst wall was smooth, glistening, and very thin. No solid tumor or association of the cyst with a nerve was found. The neck of the cyst was freed from the parietal pleura and the defect into the subarachnoid space was closed by imbricating the cyst wall and the parietal pleura with interrupted silk sutures. A small amount of talc was sprinkled over the pleura in this area to promote fibrosis. The lung was re-expanded and the incision was then closed in layers, without drainage.



A. *B.*

C.

Fig. 1.—*A.* Posteroanterior film of chest showing lesion on right; *B*, right lateral view of chest showing lesion in midposterior region over defects of vertebral bodies; *C*, cone down lateral view showing defects in posterior aspects of bodies of the sixth, seventh, eighth, and ninth thoracic vertebrae.

The postoperative course was uneventful except for moderate headache and backache, which disappeared in a few weeks. There was no reappearance of dyspnea. X-ray examination immediately following operation showed the tumor to be almost completely gone, but roentgenograms nine days and one month after the operation showed a complete recurrence. X-ray pictures one year later (Fig. 3) showed a complete regression and the patient continues to be well except for low back pain with sciatic radiation suggestive of a herniated intervertebral disc. However, the patient refuses further investigation.

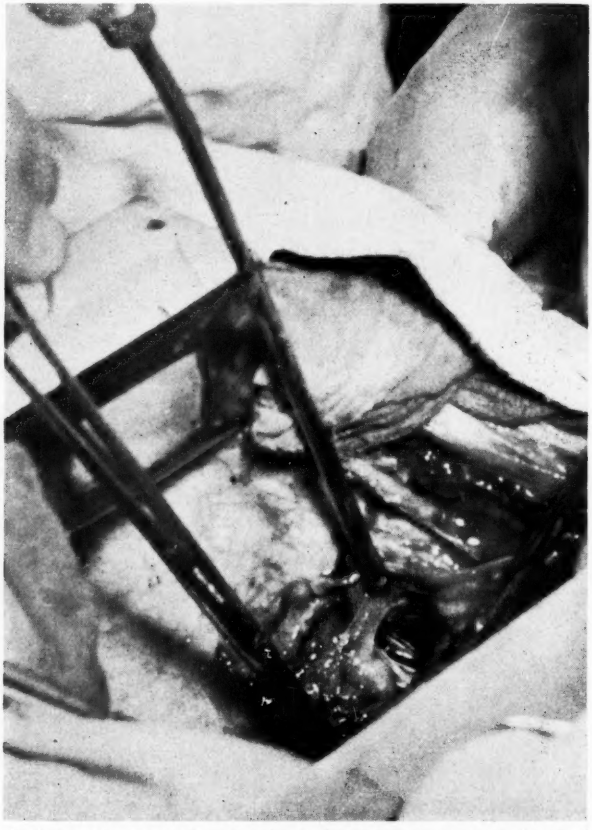


Fig. 2.—Cyst opened at operation showing defect into spinal canal at end of aspirator tip.

The incidence of intrathoracic meningocele must be rare for Thompson[1] did not mention it in his complete review of the literature on mediastinal tumors and cysts, which includes large series by Blades,[2] Heuer and Andrus,[3] and others. Heuer's[4] study of hourglass tumors of the spine did not include any cystic lesions that could be called meningoceles. Schmorl and Junghanns[5] mentioned only solid hourglass tumors as causing enlargement of the spinal nerve foramina.

Pohl[6] in 1933 reported the first case of mediastinal meningocele noted in the literature. This was in a 47-year-old woman with a right convex kyphoscoliosis of the upper thoracic spine. She also had a generalized cutaneous neurofibromatosis. The patient consulted a doctor because of the "grippe."

Dullness was found in the right upper part of the chest, an x-ray examination was ordered, and a large, oval, well-demarcated, homogeneous shadow was seen in the right upper posterior part of the chest adjacent to the spine. With a tentative diagnosis of neurofibroma, the chest was explored transpleurally. A 2 cm. defect was found in the lateral wall of the fourth thoracic vertebra through which the neck of the spinal fluid-containing cyst communicated with the spinal canal and the subarachnoid space. The cyst was emptied and the defect closed with a muscle flap. The patient died from an empyema.

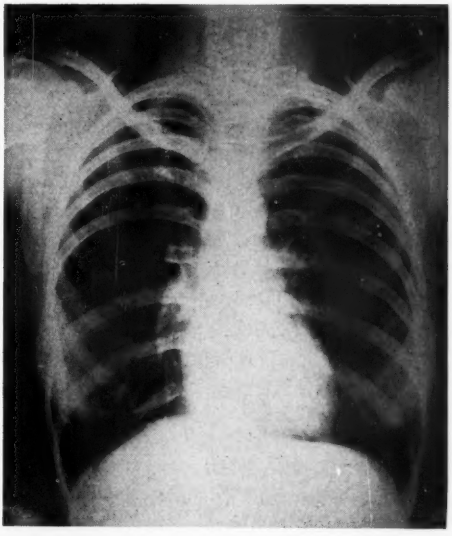


Fig. 3.—Posteroanterior film of chest one year after operation; no tumor visible.

Cabello-Campos[7] in 1946 reported two cases apparently diagnosed without operation, both in the right side of the chest. One of these patients had cutaneous neurofibromatosis and both had other congenital defects (spina bifida and congenital lung cyst). He made the statement that if one thinks of this lesion, it can be diagnosed clinically. Freedlander[8] operated on a middle-aged woman with cutaneous neurofibromatosis who had a meningocele projecting into the posterior mediastinum. One of the authors (E. B. K.) observed an intrathoracic meningocele as an incidental finding at the autopsy table.

ETIOLOGY

The frequency with which neurofibromatosis is associated with this type of meningocele is interesting. Hagelstam[9] reviewed the literature and found ninety-four cases of spinal deformity in patients with neurofibromatosis, an incidence of 7 to 20 per cent in the various series reviewed. Most of those were scolioses and kyposcolioses. Only two had spinal nerve root tumors. One of these showed marked erosion of the spinal nerve foramen and the other had eroded the neural arch. No cystic tumors communicating with the subarachnoid space were found. The vertebral defect may be congenital, but a brief survey

of textbooks[5, 10, 11, 12] reveals no mention of identical lesions. The projection of the arachnoid on the spinal nerve root through the spinal nerve foramen may be the forerunner of such a cyst.

DIAGNOSIS

The diagnosis can be made fairly easily if one investigates all posterior mediastinal tumors showing abnormalities of the vertebrae with one of the following diagnostic tests:

(1) Air myelography in the lateral decubitus position with the involved side up,

(2) Myelography with suitable radiopaque material in the lateral decubitus position with the involved side down, or,

(3) Drainage of spinal fluid following which a decrease in the size of the cyst should be demonstrable.

TREATMENT

We do not believe this lesion could have caused the patient any real distress and are inclined to believe that the symptoms were suggested only after she was told that she had a tumor within the chest. In the short preoperative stay in the hospital, she was symptomless.

Although this patient apparently has been cured, we are in doubt as to the advisability of operating on this type of lesion unless it shows progressive enlargement or causes symptoms. The defect is difficult to repair satisfactorily and might be associated with a high incidence of recurrence.

SUMMARY

A case of mediastinal meningocele is presented and the operative findings and management are described. The frequent association of this lesion with cutaneous neurofibromatosis and high incidence in women is noted. Although this is a rare lesion, methods of diagnosing mediastinal meningocele without surgical exploration are suggested. It is felt that this is an innocuous tumor which is difficult to cure surgically and that surgical interference is not indicated if the patient is asymptomatic.

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THE USE OF POLYTHENE FILM IN POSTERIOR THORACOPLASTY WOUNDS

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KARL H. PFUETZE, M.D.,‡ CANNON FALLS, MINN., AND
O. THERON CLAGETT, M.D.,* ROCHESTER, MINN.

THOUGH the modern operation of thoracoplasty for permanent collapse of the lung in pulmonary tuberculosis results in closure of cavities and changing the findings in sputum from positive to negative for tubercle bacilli in a large majority of the patients undergoing the multiple-staged operation,[1] efforts to improve the results and to extend the utility of the procedure continue. These efforts must be based on sound judgment in the choice of cases and a complete knowledge of the causes of technical failure. The failure to obtain sufficient collapse for cavitary closure may be due to one or more mechanical factors operating successively or simultaneously; for example, excessive rigidity of the lung and pleura because of extensive inflammatory fibrosis; the presence of partial bronchial obstruction with the development of a "tension" cavity; too rapid regeneration of ribs with fixation of the upper part of the chest wall before the lower supporting ribs can be removed at the next stage; adherence of the soft tissues of the chest wall to the subscapular tissues following resection of the upper two, three, or four ribs. To overcome the mechanical disadvantage presented by excessive rigidity of the lung and pleura various packs and inflatable bags have been proposed: for a "tension" cavity which fails to close after thoracoplasty, cavernostomy and other measures have been tried,[2] to prevent immediate regeneration of the ribs, which interferes with adequate collapse, formalin or Zenker's solution has been applied to the rib bed by many surgeons. It seemed to us that an agent which would prevent adhesion of the chest wall to the subscapular tissues between operative stages, if it were well tolerated by the tissues, might have some logical use in thoracoplasty. Such a substance is apparently available in polythene (polyethylene, a polymer of paraffin). Recently thin sheets of this material have been used beneath the scapula after the first stage of thoracoplasty in three patients at the Mineral Springs Sanatorium, Cannon Falls, Minn. On the basis of this experience no conclusions as to the value of the procedure can be drawn, but the desire to call attention to the possible usefulness of polythene in this manner led us to make this preliminary report.§

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‡Mineral Springs Sanatorium, Cannon Falls.

§The polythene (polyethylene) film used in this study was 0.002 inches thick and was supplied through the courtesy of the manufacturer, the Visking Corporation, Terre Haute, Ind. The manufacturer stated that it contained no impurities.

Fairly extensive experience with the use of polythene in animals has shown that the material is well tolerated by the tissues and that it undergoes no deterioration in the body, even after long periods.[3-6] The behavior of tissue of human beings in contact with the material is similar to that observed in animals. In none of our three patients was there gross evidence of acute inflammatory reaction to polythene that had been buried two weeks and microscopic preparations of specimens from two of them substantiated this observation. In one patient the tissue which had been in contact with the polythene film for two weeks showed no microscopic evidence of inflammatory change, and in the other there was moderate infiltration with lymphocytes. In addition to lymphocytes, a few foreign-body giant cells were present. It is felt, however, that these cells were not due to the presence of the polythene film but to suture material or some other foreign substance introduced at the time of operation. Other studies[3] have shown that polythene produces neither inflammatory nor foreign-body reaction.

REPORT OF CASES

A brief account of the observations made in each case follows:

CASE 1.—A man, aged 38 years, who had moderately advanced tuberculosis of the right upper lobe underwent the first stage of posterior thoracoplasty on Nov. 20, 1946. The first three ribs and half of the fourth rib were removed subperiosteally through a posterolateral incision which permitted elevation of the scapula. The wound surface was sprinkled with sulfanilamide crystals and a sheet of polythene film was fashioned to cover the subscapular surface of the chest wall. At the second stage of the procedure on Dec. 4, 1946, the incision was reopened. Healing had progressed normally. The polythene sheet had prevented the formation of any adhesions between the subscapular tissues and those of the chest wall. There was a moderate collection of serosanguineous fluid in this space, and good collapse of the chest wall had been obtained. Slight edema was present in the tissues of the chest wall which were in contact with the polythene. Subsequent microscopic examination of a section of this tissue revealed mild lymphocytic infiltration and formation of foreign-body giant cells. The wound healed by first intention.

CASE 2.—This patient was a man, aged 28 years, who had a lesion of similar extent to that encountered in Case 1. On Jan. 8, 1947, a first stage thoracoplasty through a posterolateral incision was performed. Three and one-half ribs were removed subperiosteally and sulfanilamide and polythene film were placed in the wound as in the previous case. At the second stage procedure two weeks later, healing was found to be progressing uneventfully. There were no adhesions beneath the scapula and a moderate amount of thin serosanguineous fluid was present in the subscapular space. Some edema of the fascia overlying the erector spinae muscle bundle was noted. There was no gross evidence of acute inflammatory reaction. Histologic study of a small piece of tissue from this patient failed to disclose any inflammatory reaction. A satisfactory collapse was present, and the wound healed without incident.

CASE 3.—This patient, a man 34 years old, had a first stage thoracoplasty on Feb. 5, 1947. The procedure was done in the same manner as it was in the two preceding cases. Again both sulfanilamide crystals and polythene film were placed in the wound immediately before it was closed. The wound healed with no more than the usual reaction in the tissues. At the second stage procedure on Feb. 19, 1947, there was no gross abnormality of the tissues in contact with the polythene,[1] there were no adhesions under the scapula, the usual amount of thin, serosanguineous fluid was present, and a satisfactory depression of the upper part of the chest wall had been obtained. Healing following this procedure was uncomplicated.

COMMENT

We share the view that has been expressed by others[1, 7, 8] that accumulation of fluid beneath the scapula between operative stages is desirable as a compressive force to implement atmospheric pressure and the weight of the tissues in accomplishing the desired collapse of the chest wall. The preservation of a free space beneath the scapula promotes maximal collapse by preventing fixation of the chest wall to the scapula and by permitting the accumulation of a considerable volume of fluid in the subscapular space. Polythene seems to be a material which will permit the attainment of these objectives. As to the reaction observed in the tissues in contact with the material, it is possible that sulfanilamide and suture material may have been at least partly responsible.

SUMMARY

In order to improve the results of modern multiple stage thoracoplasty to produce the permanent collapse of the lung in cases of pulmonary tuberculosis, a number of technical factors must be taken into account. One of these is the interference with collapse that results from the fixation of the upper part of the chest wall to the subscapular tissues by the formation of inflammatory adhesions after the first stage of the procedure. These adhesions can be prevented by the use of a thin sheet of polythene, an inert and apparently completely innocuous material which has been given extensive experimental and a very limited clinical trial. In the three cases which we are reporting, polythene satisfactorily served our purpose. It prevented subscapular adhesions and it did not evoke an objectionable tissue response. So many clinical and technical considerations influence both the clinical and the surgical result of thoracoplasty for pulmonary tuberculosis that no clear-cut decision is likely to be reached about the utility of this procedure. But on the basis of the logic underlying its use, further trial seems worth while.

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BRONCHIOGENIC CYST OF THE MEDIASTINUM

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IN RECENT years more has become known about the bronchiogenic cysts of the mediastinum, but observation and treatment of such cases is rare. From the publications of Blades and of Adams and Thornton most cases are asymptomatic and are found through examination by x-ray of groups of people, as in the army and navy.

At the present time the opinion is that tumors and cysts of the mediastinum should be removed, even though they cause few or no symptoms, as there is always the danger of future complications. Since this opinion has become more general, there is a marked increase in number of the operations performed (Blades). In 1937 reports of 8 cases were published by Alford. In 1940 Heuer and Andrus quoted 25 cases to which they added one of their own. In 1945 Laipply brought the number of known cases to 34. Finally in 1946 Blades reported upon 23 patients who had been operated upon in different thoracic surgery departments of the United States Army.

The first surgeon who treated a bronchiogenic cyst with success in Holland was Nyst. The cyst was found in a woman 20 years old, who had dysphagia for several years. The complaints increased, but after removal of the cyst by means of an anterior superior longitudinal mediastinotomy, according to Sauerbruch, her complaints disappeared.

In 1946 Eerland performed a successful transthoracic operation upon a woman 33 years of age. Before the operation the patient had suffered from fatigue, pain radiating from the shoulders to both arms, and attacks of dyspnea.

In 1943 we treated a bronchiogenic cyst and the case is reported here.

CASE REPORT

On Dec. 31, 1942, a 6-year-old girl was admitted to the Juliana Children Hospital and the case was diagnosed as bronchopneumonia with cavity in the right lung. She had had pertussis some years prior to this and afterward repeated attacks of bronchitis. Ten days before admission to the hospital she was ill with high temperature, spells of coughing, and dyspnea. Two days before admission the condition had grown much worse in spite of chemotherapy. She expectorated a greenish mucopurulent secretion, lost her appetite, and became emaciated. There was no tuberculosis in the family.

On examination the child was found to be short of breath and cyanotic. The mucous membranes were cyanotic. There was no jaundice and no evidence of anemia. Lymphatic glands were palpable in the groins. The turgor of the skin was good. The condition of the heart was normal. In the lungs only bronchitic murmurs were audible. The abdomen and limbs were normal. The temperature fluctuated between 39 and 40° C. The pulse frequency was 140-160, but regular. Upon examination the greenish mucopurulent sputum showed no

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tubercle bacilli. Urine was normal. The blood sedimentation rate was 55 after one hour, 75 after two hours. Red blood count on admission was 4,000,000 with hemoglobin 90 per cent; the white blood count 21,400 (6 per cent stab neutrophilic, 80 per cent segmented neutrophilic, 11 per cent small lymphocytes, 2 per cent monocytes, and 1 per cent basophilics). The thrombocytic count was normal.

An x-ray picture of the chest showed a shadow in the right lower lobe, probably of pneumonic or pleuritic origin. In the upper part of the chest a sharply outlined density, the size of a goose egg, protruded from the mediastinum to the upper lobe. The oblique x-ray view showed compression of the trachea directly above the bifurcation. The right main bronchus was also compressed, though less than the main bronchus (Fig. 1). On a bronchogram with lipiodol there was no bronchiectasis in the right lung.

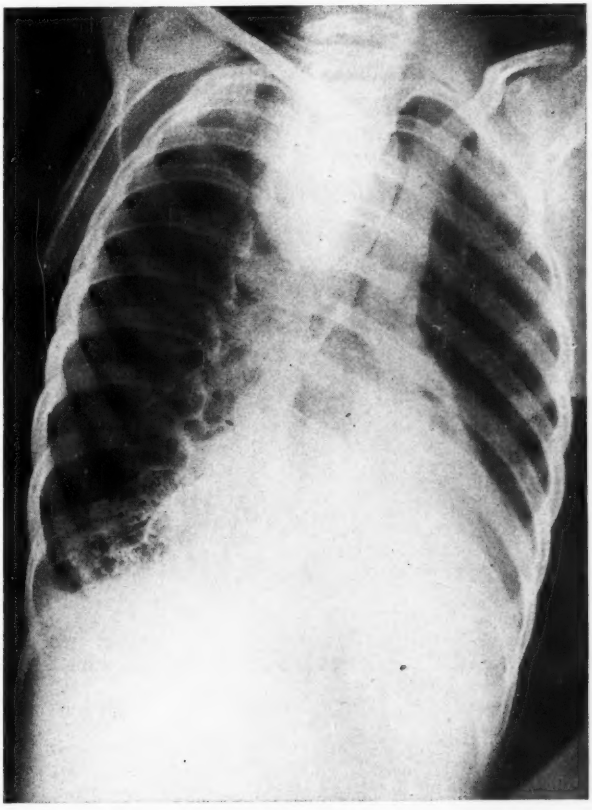

Fig. 1.—Compression of the trachea (oblique x-ray) directly above the bifurcation; compression of the right main bronchus.

On the basis of the x-ray examination it was decided that the tumor of the mediastinum was benign (dermoid cyst). Through the compression of the trachea and the right main bronchus, the tumor caused repeated attacks of retention in the right lung with symptoms of pneumonia. Surgery was indicated.

Operation.—Operation was performed on Jan. 8, 1943 (J. E.). Nitrous oxide oxygen-ether anesthesia was administered after premedication with atropine (¼ mg.) and rectidon.

An anterolateral incision was made on the right side in the third intercostal space. After the opening of the chest the lung collapsed very well. The tumor in the mediastinum, protruding in the pleural cavity, was distinctly visible. The tumor was sharply outlined and gave the impression of a cyst. After splitting the pleura mediastinitis in longitudinal direction under the phrenic nerve the cyst was freed for the greater part by blunt dissection. A much harder tumor, the size of a hazelnut, was attached to the upper side of the large cyst. In attempting to divide the large cyst from the small tumor, a small perforation was accidentally made, from which a thick, gelatinous and viscous liquid oozed. The perforation was closed. Subsequently we succeeded in closing the perforation and removing the cyst with its smaller appendix. There was no bleeding from the cyst bed. The cyst was located dorsal to the vena cava superior above the heart and ventral to the esophagus. The trachea was compressed to the left side. The right main bronchus was also compressed by the underpart of the cyst. The mediastinum was closed with chromic catgut. The chest was closed without drainage.

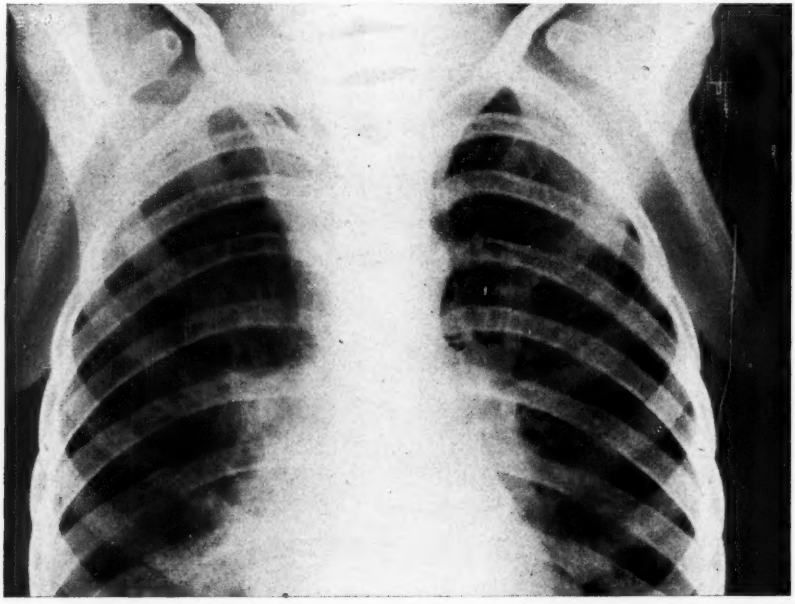

Fig. 2.—X-ray picture one month after the operation.

The day after the operation the dyspnea had totally disappeared. All symptoms of pneumonia disappeared within five days. The temperature became normal after three days.

The x-ray picture taken after the operation showed in the place where the cyst was localized, a fluid level. This level had disappeared after one month. The alterations in the lower lobe disappeared at the same time (Fig. 2).

The child was dismissed in good health. Further checkups on Aug. 10, 1944 and on April 19, 1946, were entirely satisfactory. The child's good health had continued and she had suffered no attacks of bronchitis.

Pathologic Anatomy.*—

Macroscopic: The diaphanous cyst was goose egg sized and contained a very thick, viscous liquid. The wall was very thin, except on the place where a small hazelnut-sized lump was seen. The wall of this lump was considerably thicker than the rest of the cyst.

*Dr. Wyers.

Between the hollow of this smaller lump, containing the same viscous mass, and the large one, there was a large communication.

Microscopic: It was impossible to make slides of the contents of the cyst. The different liquids for impregnation did not permeate. Some polynuclears and perhaps some eosinophiles were recognized. Other cells were not recognized.

The thin part of the cyst wall was composed of lined connective tissue, on the inner side clothed with regular respiratory epithelium (columnar ciliated). The cilia were long and very well visible. Under the epithelium there was connective tissue with many and wide, very

Fig. 3.—Hazelnut-sized lump with three bent pieces of cartilage.

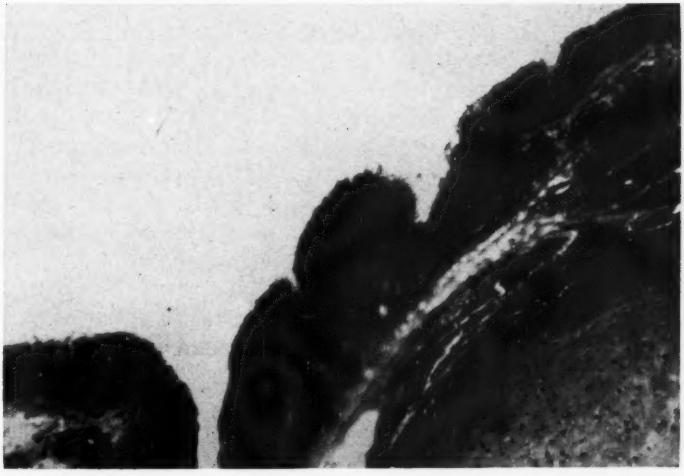

Fig. 4.

thin-walled blood vessels. In the connective tissue there was infiltration of lymphocytes, plasma cells, and polymorphonuclears. A small area of mucous glands of very regular structure was found in the deeper layers. The protoplasm of these glands was slight vacuolar.

In the more solid part (lump) there were three bent pieces of cartilage (Fig. 3). The cartilaginous tissue was of a regular structure and surrounded by perichondrium. In the small interspaces between the ends of the cartilages there were many mucous glands extending behind the cartilages. There was no muscle tissue (Fig. 4).

Conclusion was bronchiogenic cyst of the mediastinum.

Chemistry of the cystic fluid: The test of Rivalta with 10 times diluted cystic fluid gave negative findings. The undiluted liquid was too viscous to test it in any other way. The test of Benedikt with 10 times diluted fluid revealed negative findings. After boiling the fluid with an equal volume 5 per cent HCl, the test of Benedikt was slightly positive.

The fluid diluted 1:15 with acetic acid in cold air gave a bubbling. The Kjeldahl test with 75 times diluted liquid: total nitrogen, 40.50 per cent; nonprotein nitrogen, 17.25 per cent; protein nitrogen, 23.25 per cent; total protein, 14.50 per cent; phosphorus, 98 mg. per cent.

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